A TEXT-BOOK OF
ORGANIC CHEMISTRY

BY

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ENGLISH EDITION

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PREFACE TO SECOND ENGLISH EDITION

In preparing the second English edition of Schmidt's *Organic Chemistry*, the whole of the text has been carefully revised, with the two-fold purpose of incorporating the main advances which have been made in the subject since the issue of the first edition in 1926 and of avoiding any appreciable increase in the size of the book.

As a result of various suggestions put forward by reviewers and readers of the first edition, considerable changes have now been made in the preliminary general section Students of organic chemistry do not refer to a treatise of this type for detailed information on analytical processes or physical methods of determining molecular weights By curtailing the space devoted to these subjects, room has been made for the discussion of a number of topics of more general interest, including recent work on addition to conjugated systems, the electronic theory of valency, the mechanism of racemisation, epimerisation, conditions for enantiomorphism, isomerism due to restricted rotation around a single bond, asymmetric decomposition, spiro-compounds, the stereochemistry of nitrogen and sulphur, the Beckmann rearrangement, tautomerism, the parachor, polar properties of organic compounds, and factors influencing the magnitude of optical rotatory power This extension of subject-matter has necessitated an increase in the general section of some 29 pages, but the change will, it is hoped, considerably enhance the value of the book to third and fourth year students For permission to use the two illustrations on pages 5 and 6, which are taken from Cumming and Kay's *Quantitative Analysis*, I am indebted to Dr S A Kay A number of other new diagrams and figures have also been prepared for this part of the book.

It is only possible to indicate a few of the many alterations which have been made in the text dealing with the systematic treatment Some of the more important of these refer to recent progress in the chemistry of the sugars, purines, terpenes, sterols, bile acids, condensed pyrroles, alkaloids and proteins A number of new sections or paragraphs have also been introduced, such as those dealing with synthetic methanol and synthol, phosphatides, catechins and enzymes. A considerable proportion of these last-named alterations have been

taken in part or whole from the fourth German edition (1929), with which the new text has been carefully compared. In other parts of the book fresh material has been added, either to draw attention to new developments, as in the case of the Diels and Alder reaction in the sesquiterpenes, vitamins, and the aporphine group of alkaloids, or for the purpose of correlating and extending information already contained in the earlier edition, as in the case of growing chain effect in benzene substitution, and the relationship between terpenes and the isoprene structure. The constitution of piperine has now been dealt with more completely by the introduction of a synthesis of piperic acid.

As in the previous edition, an effort has been made to avoid the use of vague statements such as that a given reaction is brought about "by oxidation" or "by reduction". Except in general cases an attempt has been made to indicate the actual reagent employed. The text has been very fully indexed and its value for purposes of reference augmented by an increase in the number of melting-points and boiling-points listed.

In placing the second English edition before the public, I am glad to acknowledge the helpful criticism of reviewers and a number of former students, which has been of great assistance in adapting the German text for use by English-speaking chemists. I also wish to record my indebtedness to my wife, who has collaborated with me in preparing the book for the press, to Dr J M Gulland for invaluable help in revising the pages on the morphine alkaloids, to Dr N Campbell in dealing with the Beckmann rearrangement, and to Dr J Harrower and Dr A McLean for aid in proof-reading.

H GORDON RULE

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LIST OF ABBREVIATIONS

ABBREVIATIONS	JOURNALS
Am C J	American Chemical Journal
Ann	Liebig's Annalen der Chemie
Ann Chim Phys	Annales de Chimie et de Physique
Ann Rep Chem Soc	Annual Reports of the Chemical Society
Arch Pharm	Archiv der Pharmazie
Ber	Berichte der deutschen chemischen Gesellschaft
Biochem J	Biochemical Journal
Biochem Zeitsch	Biochemische Zeitschrift
Biochem Z	Biochemische Zeitung
Bull Soc	Bulletin de la Société Chimique à Paris
C	Chemisches Zentralblatt
Ch Zeit	Chemiker Zeitung
C r	Comptes rendus de l'Académie des Sciences
Gazz	Gazzetta Chimica Italiana
Helv Chim Acta	Helvetica Chimica Acta
J Am C S	Journal of the American Chemical Society
J Biol Chem	Journal of Biological Chemistry
J C S	Journal of the Chemical Society
J C S, A	Abstracts of the Chemical Society
J Ind and Eng Ch	Journal of Industrial and Engineering Chemistry
J Physiol	Journal of Physiology
J. Phys Chem	Journal of Physical Chemistry
J pr Ch	Journal für praktische Chemie
J S C I	Journal of the Society of Chemical Industry
Monats	Monatshefte für Chemie
Pogg Ann	Poggendorf's Annalen der Physik
Proc Chem Soc	Proceedings of the Chemical Society
Proc Roy Soc	Proceedings of the Royal Society
Trans Farad Soc	Transactions of the Faraday Society
Z. anal Ch.	Zeitschrift für analytische Chemie
Z ang Ch	Zeitschrift für angewandte Chemie
Z Ch	Zeitschrift für Chemie
Z Elek.	Zeitschrift für Elektrochemie
Z phys Ch	Zeitschrift für physikalische Chemie
Z physiol Ch	Zeitschrift für physiologische Chemie

ORGANIC CHEMISTRY

Introduction

THE remarkable variety of carbon compounds which could be prepared from plant and animal sources began to arouse interest at an early date, and this led to systematic investigations into their mode of origin and the manner in which they could be transformed one into another. It was not until the eighteenth century, however, that the first results of importance were obtained at the hands of Lavoisier. The work was found to present peculiar difficulties and to require a special laboratory technique, hence at the beginning of the nineteenth century it was severed completely from inorganic chemistry and considered as a separate branch of chemical science.[1] The name of *Organic Chemistry* originated in the belief that compounds of this type could not be prepared artificially in the laboratory, but were formed solely in living organisms under the influence of a mysterious agency termed Vital Force. Experimental evidence at first lent support to this theory, in so far that all attempts to build up such substances from materials not themselves obtained from living organisms were unsuccessful.

Faith in the Vital Force theory was shaken in 1828 by the discovery of Wöhler[2] that urea, one of the most characteristic products of animal metabolism, could be prepared from the inorganic constituents cyanic acid and ammonia.

Other syntheses followed, until it was proved beyond all doubt that the same chemical forces operated in the organic as in the inorganic world, and the assumption of a vital force responsible for the production of carbon compounds in the organism was therefore superfluous. Nevertheless there are many substances of plant and animal origin, including the very widespread class of proteins, which have so far eluded artificial preparation. Various reasons may be put forward to explain this lack of success. Not only has the precise chemical composition of the proteins yet to be determined, but even the mode of union of the atoms in these compounds is still unknown. Nor have we

[1] An effort had already been made in the second half of the seventeenth century to separate organic from inorganic chemistry by classifying each substance according to its origin as mineral, animal, or vegetable (Kopp, *Geschichte der Chemie*, 4, 241). [2] Wöhler, "Ueber künstliche Bildung des Harnstoffs," *Pogg. Ann.*, 1828, 12.

any clear conception of the physico-chemical conditions under which these substances are produced in the living organism On the other hand, the brilliant researches on the polypeptides carried out by Emil Fischer point the way to the artificial preparation of compounds (albumoses and peptones) which are fission products of the proteins, and are therefore closely related to them [1]

Although we still speak of organic and inorganic chemistry, the terms are retained solely for convenience of reference The peculiarities of organic compounds depend only on the nature of their principal constituent carbon, and the wide extent of organic chemistry is a direct consequence of the unique combining capacity of the carbon atom Not one of the other elements even approaches carbon in its ability to unite with itself, atom by atom, to form open and closed chains, and as a result, the number of known carbon compounds, now well over 250,000, exceeds that of the compounds of all the other elements put together

Organic Chemistry is thus to be defined as the chemistry of carbon compounds [2]

As the majority of organic compounds resulting from plant and animal activity consist only of carbon, hydrogen, oxygen and less frequently nitrogen, these elements have been termed organogenetic It is comparatively rare to find organic substances in nature containing sulphur and phosphorus, although by artificial means the introduction of practically any element can be effected

[1] E Fischer, *Ber*, 1906, 39, 531 [2] Carbon itself and a few of its simple compounds, such as carbon dioxide and carbonates which are of frequent occurrence in the mineral world, are usually described in text books on inorganic chemistry and are not included here

Analytical Methods

RELATIVELY few organic compounds are distinguished by reactions sufficiently characteristic to serve as a basis for their qualitative identification. For the separation of organic substances from mixtures there is therefore no general procedure known comparable to the systematic analysis of inorganic chemistry.

In many cases the physical properties of a substance such as smell, crystalline form, melting-point, boiling-point, or optical rotation enable it to be identified. More often it is necessary to determine its composition, first qualitatively and then quantitatively. Since no convenient method has been developed for the estimation of oxygen this element is always determined indirectly, after the quantitative estimation of the other elements present.

QUALITATIVE ANALYSIS OF ORGANIC COMPOUNDS.

Carbon and Hydrogen.—Carbon may be detected in many cases by heating the dry substance on platinum foil or in a porcelain crucible. The majority of compounds (*e.g.*, starch, sugar) blacken under these conditions with the separation of carbon. Compounds which volatilise without decomposition are tested by oxidising the carbon to CO_2; the dried substance is mixed with several times its volume of copper oxide, which has previously been strongly ignited, and the mixture heated in a small dry glass tube. The formation of CO_2 can be confirmed by leading the products of combustion into lime- or baryta-water. At the same time the deposition of moisture on the colder parts of the tube indicates the presence of hydrogen in the substance under investigation.

Oxygen.—Up to the present no general method has been devised for the detection of oxygen in organic compounds.

Nitrogen.—(*a*) In many cases the presence of nitrogen may be recognised by the production on heating of the unpleasant smell of singed hair or feathers.

(*b*) In a limited number of nitrogenous substances the nitrogen can be detected by heating with soda-lime, when ammonia is evolved and may be recognised by its smell and other characteristic reactions. Nitro-compounds, amongst others, fail to give this test.

(*c*) The most reliable and sensitive method is that of Lassaigne, which consists in heating the organic substance with potassium or sodium, and converting the cyanide so formed into Prussian blue.

The substance is strongly heated in a test-tube with metallic sodium (or better still potassium), and the hot tube broken by dipping into a little water. After filtration, the aqueous extract is heated for a short time with sodium hydroxide and ferrous sulphate solutions, acidified with hydrochloric acid, and treated with a few drops of a solution of ferric chloride. An insoluble precipitate of Prussian blue or a bluish-green coloration shows the presence of nitrogen in the substance tested.[1]

Sulphur.—(*a*) On heating sodium with sulphur compounds, sodium sulphide is formed. The latter is confirmed by dissolving the product of reaction in water and testing with sodium nitroprusside (purple coloration), with a silver coin (dark brown stain), or with lead acetate solution (dark precipitate).

(*b*) Sulphur may frequently be recognised by boiling the substance (*e.g.*, albumin) with a solution of lead hydroxide in alkali, when black lead sulphide is formed.

(*c*) Easily volatile substances are best heated in a closed tube with fuming nitric acid at about 200 to 300° C. (see below). Sulphur is thus oxidised to sulphuric acid, which may be tested for by dilution with water and the addition of barium chloride.

In the same way **phosphorus** may be recognised by oxidation to phosphoric acid and subsequent addition of ammonium molybdate or magnesia mixture.

Halogens.—Only in rare cases (*e.g.*, hydrochlorides of bases, acid chlorides and similar easily decomposable compounds) can the halogens be tested for by direct precipitation with silver nitrate. The reason for this is that most organic halogen compounds are non-electrolytes, *i.e.*, their solutions, unlike those of inorganic halides, contain no free halogen ions. Thus chloroform may be boiled with silver nitrate without the formation of any precipitate of silver chloride.

The presence of halogens may often be proved by mixing some of the substance with freshly ignited copper oxide, and by means of a loop of platinum wire introducing a little of the mixture into a bunsen flame. In the presence of chlorine the flame is coloured first blue and then green. Bromine and iodine compounds produce a green coloration.

All organic substances containing halogen yield insoluble silver halide when they are oxidised by heating in a sealed tube with nitric acid and silver nitrate, or when the organic substance is decomposed by ignition with halogen-free calcium oxide and the product subsequently dissolved in water, acidified and treated with silver nitrate.

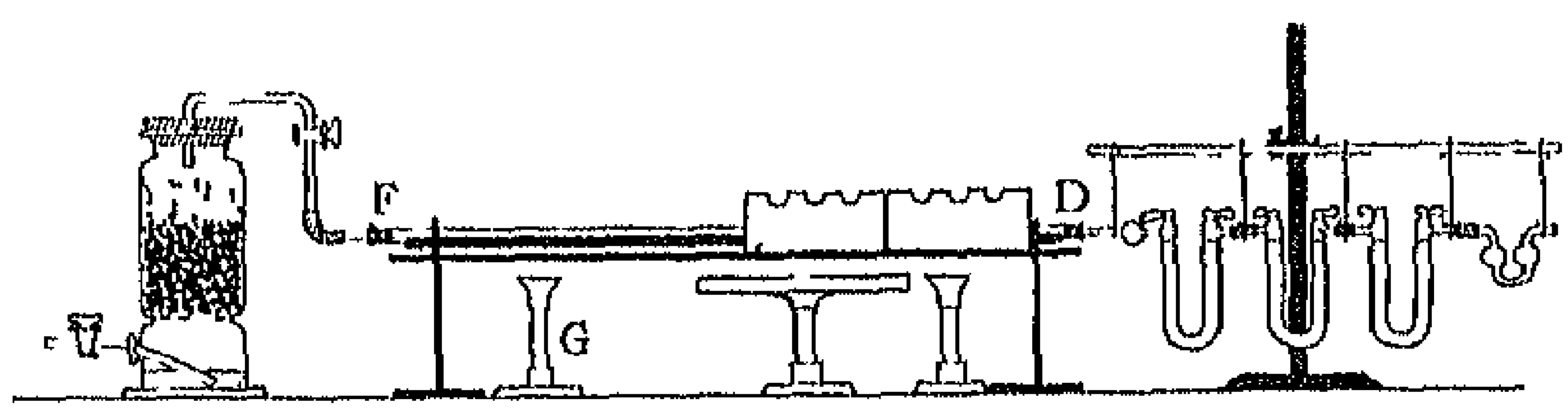
Detection of Metals.—It is not always possible to test for metals directly by means of the usual reagents. It is best therefore in all cases to decompose the organic substance by ignition or oxidation, and then to test for metals in the routine manner.

[1] For procedure in cases where the detection of nitrogen offers special difficulty, see Kehrer, *Ber.*, 1902, 35, 2523.

QUANTITATIVE ANALYSIS OF ORGANIC COMPOUNDS[1]

Estimation of Carbon and Hydrogen (Combustion) — Many elebrated names are linked with the history of this branch of organic nalysis. Beginning with Lavoisier, the problem was investigated in urn by Berthollet, Saussures, Davy, and finally and most successfully y Liebig,[2] who developed a method which with small modification is till in use to-day. The details of the process are fully described in ext-books of analytical chemistry and only the fundamental principles ill be considered here.

A weighed amount (0.15 to 0.30 gm.) of the substance is heated ith an oxygen compound (copper oxide, lead chromate) capable of eadily yielding up its oxygen at a higher temperature, by which means rbon is converted into carbon dioxide and hydrogen into water. The vo products of oxidation are then collected in a suitable apparatus. or the absorption of the water vapour produced in a combustion, a



Drying tower FIG. 1 Absorption tubes

-tube filled with calcium chloride is employed. Carbon dioxide is sorbed by means of potash in the apparatus described by Liebig, or e of its later modifications. Soda-lime is even better for this purpose. e absorption tubes are carefully weighed before and after the com-stion. The increase in weight of the calcium chloride tube divided 8.9364 ($H_2 : H_2O = 2.016 : 18.016$) gives the amount of hydrogen, d the increase in weight of the potash tube multiplied by 3/11 $CO_2 = 12 : 44$) gives the amount of carbon in the substance analysed.

If the compound contains nitrogen, the combustion gases before ving the tube are passed over a copper spiral heated to redness, in ler to reduce any nitric oxide formed. Fused lead chromate is ployed instead of copper oxide in the presence of sulphur or halogens, is retaining as sulphate or chloride of lead the sulphur dioxide or orine which would otherwise be absorbed in the potash tubes. If logens are present and sulphur absent, the combustion may be carried t with copper oxide in combination with a silver spiral, the latter is ot cool and serves to remove the halogens.

See also M. Dennstedt, *Anleitung zur vereinfachten Elementaranalyse*, 4th edition, Hamburg,) [2] Liebig, "Ueber einen neuen Apparat zur Analyse organischer Körper und über die mmensetzung einiger organischen Substanzen," *Pogg. Ann.*, 1831, 21, 1.

In the presence of alkalis or alkaline earths, which would otherwise hold back carbon dioxide, a mixture of lead chromate and potassium bichromate is employed, the chromic acid then decomposes the carbonates formed

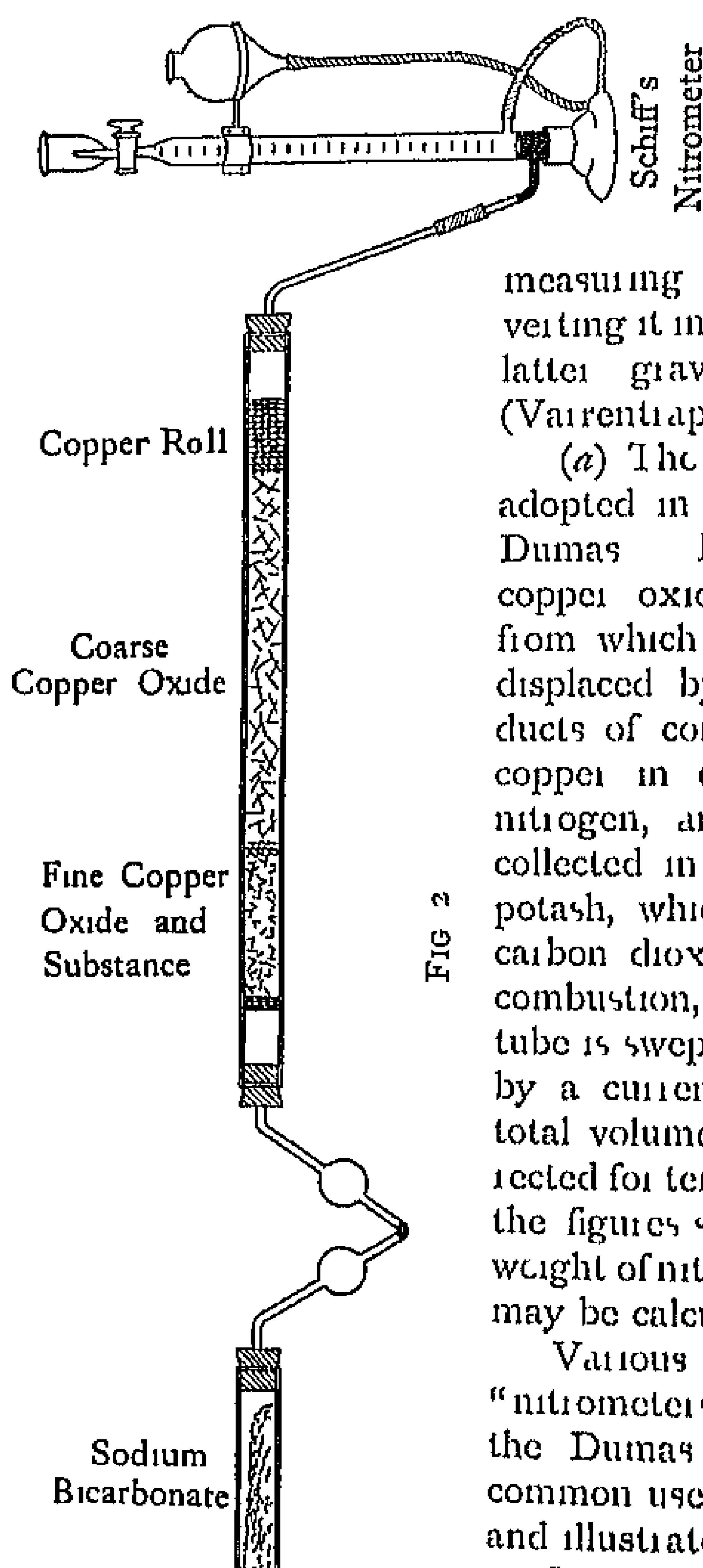


Fig 2

Estimation of Nitrogen—Nitrogen in an organic compound can be determined either by eliminating it in the elementary state and measuring its volume (Dumas), or by converting it into ammonia and estimating the latter gravimetrically or volumetrically (Varrentrapp-Will, Kjeldahl)

(*a*) The procedure almost universally adopted in scientific laboratories is that of Dumas The substance is mixed with copper oxide and combusted in a tube from which all the air has been completely displaced by carbon dioxide[1] The products of combustion are led over red-hot copper in order to reduce any oxides of nitrogen, and the free nitrogen is then collected in a graduated tube over strong potash, which removes the accompanying carbon dioxide After completion of the combustion, any nitrogen remaining in the tube is swept over into the measuring tube by a current of carbon dioxide, and the total volume of the gas read off and corrected for temperature and pressure From the figures so obtained the percentage by weight of nitrogen in the original compound may be calculated

Various forms of measuring tubes or "nitrometers" are available for use with the Dumas method, the type in most common use being that devised by Schiff, and illustrated in Fig 2.

In spite of all precautions it is never possible to sweep out the last traces of air from the tube, and there remains always a residue of at least 0 2 to 0 5 c c The errors produced in this way are approximately balanced by the similar difficulty of removing the last traces of nitrogen from the combustion tube at the finish

[1] The atmosphere of carbon dioxide may be generated by heating dry sodium bicarbonate or magnesite, or by means of a Kipp's apparatus

(b) *Kjeldahl's Method*[1]—This process is employed mainly in technical analysis, where a large number of similar determinations have to be carried out in the shortest possible time. For this purpose it excels all other methods of nitrogen estimation. The substance is heated with concentrated sulphuric acid, together with the addition of potassium permanganate, mercuric oxide or mercury. Under these conditions the organic substance is decomposed and nitrogen converted into ammonia. The latter is determined by diluting the strongly acid liquid with water, making alkaline with excess of sodium hydroxide and distilling over into a measured quantity of standard acid. After titrating back, the amount of ammonia may be calculated in the usual way. This method fails with a large number of organic substances, including pyridine and quinoline derivatives and compounds containing nitrogen linked to a second nitrogen atom,[2] although sometimes a small modification in the conditions makes successful analysis possible.[3] The process is particularly suitable for the estimation of nitrogen in plant and animal products. In academic work it will also be found of advantage in the analysis of compounds such as proteins, where, owing to the relatively low nitrogen content, a disproportionate amount of carbonaceous material has to be oxidised for each determination.

In each of the foregoing methods nitrogen is determined separately. Methods are also in existence for the simultaneous estimation of nitrogen and carbon or hydrogen, but are not yet in common use.

Estimation of Sulphur, Phosphorus and Halogens.—Vigorous oxidation of an organic compound containing *sulphur* converts the latter into sulphuric acid, which may then be precipitated by barium chloride. The oxidation may be carried out:—

(*a*) In the dry way by heating with a mixture of potassium chlorate and sodium carbonate, or potassium hydroxide and nitre, or by heating with sodium carbonate and mercuric oxide. More recently sodium peroxide has been used as the oxidising agent.[4]

(*b*) In the wet way by heating in a sealed tube with concentrated nitric acid at 150-300° (Carius).

(*c*) A reliable modern method[5] is to heat the substance in a stream of oxygen, using fine platinum gauze as catalyst. The sulphur dioxide evolved is absorbed in a solution of bromine in sodium hydroxide, by which it is oxidised to sulphuric acid.

In order to determine *phosphorus* in an organic compound, the latter may be oxidised to phosphoric acid and estimated with magnesia

[1] *Z. anal. Ch.*, 1883, 22, 366. See also Villiers and Talon, *C.*, 1919, IV, 559. [2] For the analysis of compounds containing nitrogen to nitrogen linkings, compare Flamand and Prager, *Ber.*, 1905, 38, 559. [3] Nitro- and cyano compounds must first be mixed with sugar, and nitrates with benzoic acid, compare *Ber.*, 1894, 27, 1633; Dyer, *J. C. S.*, 1895, 67, 811, 817; *C.*, 1898, II, 312. [4] Pringsheim, *Ber.*, 1903, 36, 4244; 37, 2155. [5] H. Apitzsch, *Z. ang. Ch.*, 1913, 26, 503.

mixture For this purpose the methods of oxidation already described above are suitable

In some cases it is convenient to oxidise sulphur and phosphorus in the wet way, by use of potassium permanganate and potassium hydroxide, or with bichromate and hydrochloric acid[1]

Similarly in the estimation of the *halogens* it is usual to oxidise the organic substance completely, before converting the halogen into silver halide In solutions of hydrochlorides of organic bases the halogen can be directly precipitated with silver nitrate

(*a*) From early times halogen has been estimated by decomposing the organic substance with halogen-free quicklime at a high temperature The simplest procedure is to mix the substance with lime and to heat in a short, narrow combustion tube When the reaction is complete the contents of the tube are dissolved in nitric acid, carbon and splinters of glass are filtered off, and the halide precipitated with silver nitrate or determined volumetrically This method is of universal application, although inconvenient in the case of volatile substances, owing to the longer tube required and the larger quantity of lime to be brought into solution

(*b*) A method which leapt at once into favour is that first suggested by Carius in 1860, improved in 1865, and five years later[2] modified to the form commonly in use to-day It resembles the estimation of sulphur (see above) in that the substance is heated with concentrated nitric acid and silver nitrate in a sealed tube at 200-300°, the halogen being obtained directly as silver halide This method of estimating halogens has practically displaced all others from the field

Sodium peroxide has also been proposed for the determination of halogen

(*c*) Attention has lately been drawn to a method recommended by Baubigny and Chavanne, in which the substance is heated to 130-140° with a mixture of potassium bichromate and concentrated sulphuric acid, in the presence of silver sulphate or nitrate[3] The escaping chlorine or bromine is absorbed in a sulphite solution, and titrated as halogen acid, while iodine remains behind as hydriodic acid In the case of chlorine and bromine estimations, D Vorländer[4] substitutes mercuric oxide or nitrate, the silver salt being necessary only in the presence of iodine A simple and rapid method of accurately determining chlorine and bromine by oxidation with chromic acid mixture, and trapping the liberated halogen in alkaline hydrogen peroxide, has been devised by P W Robertson[5] These modifications are found to be of general application and—except for the analysis of volatile

[1] Messinger, *Ber*, 1888, 21, 2914 [2] *Ber*, 3, 697 (1870) The practical details of the method were subsequently somewhat altered by F W Kuster, *Ann*, 1895, 285, 340 See also Secker and Mathewson, *Chem News*, 1911, 103, 61 [3] H Emde, *J C S*, 1911, A, ii, 532 [4] D Vorlander, *Ber*, 1919, 52, 308 [5] P. W Robertson, *J C S*, 1915, 107, 902

substances—may eventually displace the Carius method from laboratory practice

(*d*) A simple method of estimating halogen in organic compounds,[1] especially benzene derivatives, consists in the combustion of the substance in a Dennstedt apparatus, the halogens being absorbed in alkaline sulphite and subsequently titrated

(*e*) It is also possible to reduce the halogen in many compounds (*e g* the halogen substituted fatty acids) by means of nascent hydrogen In these cases the substance is treated with water and sodium amalgam, and shaken frequently during the course of several hours The aqueous solution is then decanted from the mercury, the latter washed with water and the combined solutions acidified with nitric acid The halogen is estimated either volumetrically or gravimetrically Those compounds containing halogen attached to an aromatic ring do not lose it under this treatment. On the other hand, the method of Stepanow, as modified by Bacon, for the estimation of halogen by reduction with sodium and alcohol gives satisfactory results even with aromatic derivatives[2]

Estimation of Metals and Inorganic Acids—In most cases the metals are determined by routine inorganic analysis, after the organic substance has been decomposed either by heating to redness, or by oxidation in the wet or dry way, according to the nature of the metals present

Frequently the metals may be estimated simultaneously with carbon and hydrogen, by combusting the substance in a porcelain boat in a current of oxygen (*e g* , silver salts of organic acids)

The inorganic acids present in salts of organic bases can usually be determined in the customary manner

Estimation of Oxygen —The oxygen content of an organic compound is always estimated by difference

Dennstedt's Method of Analysis[3]

In the Dennstedt method, which has to some extent displaced that of Liebig, the combustion is carried out in oxygen in the presence of platinum as catalyst The products of combustion, water and carbon dioxide, are trapped in weighed tubes containing calcium chloride and soda-lime respectively

Compounds containing *nitrogen* yield in addition nitrogen peroxide, which must not be permitted to pass into the absorption apparatus The gases are therefore led over suitably heated lead dioxide, when the nitrogen peroxide is retained as lead nitrate If the substance contains *sulphur*, this element becomes oxidised to sulphur dioxide and trioxide, both of which are absorbed by the lead peroxide to form lead sulphate Since the latter may be extracted quantitatively, it is possible to estimate the carbon, hydrogen and sulphur simultaneously

[1] K Dachlauer and C Thomsen, *Ber* , 1924, 57, 559 F Arndt, *ibid* , p 763 [2] Stepanow, *Ber* , 1906, 39, 4056 C W Bacon, *Chem News*, 1909, 99, 6 Walker and McRae, *J Am C S*, 1911, 33, 598 [3] M Dennstedt, *Anleitung zur vereinfachten Elementaranalyse*, Hamburg

Similarly lead dioxide completely absorbs *chlorine* and *bromine*, which are liberated on combustion either as such or as the hydrogen compounds. *Iodine* is always eliminated in the free state and removed by means of "molecular" silver contained in a porcelain boat. If the substance under consideration is free from nitrogen and sulphur, the amount of iodine is given directly by the increase in weight of the boat. This is also the simplest way of estimating chlorine or bromine in the absence of nitrogen. In cases where nitrogen or sulphur, or both, are present in addition to halogens, the silver halide formed is mixed with nitrate or sulphate. For the simultaneous estimation of halogen, or halogen and sulphur, under these conditions, reference should be made to the original paper of Dennstedt already quoted.

Simplified methods of micro analysis for organic compounds have also been submitted to careful investigation in the last few years.[1]

In principle these do not differ much from the routine methods, but are carried out with the use of very small quantities. Carbon and hydrogen are oxidised with copper oxide and lead chromate in a stream of oxygen. The CO_2 and H_2O are absorbed in the usual way, and nitrogen estimated volumetrically by the Dumas method. The few milligrammes of the substance employed are weighed on a micro balance, and the whole apparatus is much reduced in size. The advantages of the method lie not only in a saving of gas and time but above all of material. The last point is of the greatest importance, more particularly since research in organic chemistry is extending more and more to biochemical processes, from which in many cases only minute quantities of valuable products can be isolated.

Calculation of Empirical Formulæ

The formula of the substance is deduced from the percentage composition, as found by analysis, in the same way as with inorganic compounds. The percentage figures are first divided by the atomic weights of the elements to which they have reference; the quotients thus obtained show the relative proportions in which the atoms are combined together. On using the smallest of these quotients as a divisor for the others, values are arrived at which either approximate to whole numbers or do so after further simple multiplication. The formula finally deduced should be in accordance with the Law of Even Numbers.

Example.—The analysis of a substance consisting of carbon, hydrogen, nitrogen, chlorine and oxygen gave

	44.05% C,	7.38% H,	10.18% N,	26.19% Cl,	and by difference	12.20% O.
The divisions	$\frac{44.05}{12}$,	$\frac{7.38}{1}$,	$\frac{10.18}{14}$,	$\frac{26.19}{35.5}$,		$\frac{12.20}{16}$ yield the
figures	3.59,	7.38,	0.73,	0.74,		0.76
These divided by 0.73 give						
	4.92,	10.01,	1.0,	1.01,		1.04

From which the simplest formula is $C_6H_{10}ONCl$.

[1] See F. Pregl, *Quantitative Organic Microanalysis*, translated by E. Fyleman (Churchill, 1924).

The simplest formula obtained in this way is termed the *empirical formula*, and does not always correspond to the real molecular weight, which may prove to be some higher multiple thereof.

After discovering the percentage composition of a substance and with it the proportions in which the atoms are united together, the next problem is to ascertain the true molecular weight.

DETERMINATION OF MOLECULAR WEIGHT—MOLECULAR FORMULA OF AN ORGANIC COMPOUND.

It is frequently possible to deduce the probable molecular weight of a compound from the reactions by which it is formed. In other cases the information can be gained from a detailed chemical investigation of the nature of the substance. In most instances, however, the best results are given by physical methods.

Determination of Molecular Weight by Chemical Methods

It should be said at once that an absolutely sure method of determining molecular weights by purely chemical means is not available. It is only possible to eliminate certain of the values in question and to estimate with some probability the actual size of the molecule.

For this purpose derivatives of the substance must be prepared possessing an atom or radical capable of being quantitatively determined, from the proportion of which the molecular formula of the derivative may be calculated and hence that of the parent substance.

Salt forming compounds, such as acids and bases, lend themselves best to this end. In the case of acids the determinations are carried out preferably with the silver salts, because these are usually of normal composition and easily analysed. In addition it is necessary to know the basicity of the acid, which may be ascertained from an examination of the esters or salts. As will be seen later (p. 82) the electrical conductivity also gives valuable information on this point.

For similar reasons the determination of the molecular weight of a base is carried out by means of its platinum salt, which is generally of the type of ammonium chloroplatinate, $(NH_3)_2H_2PtCl_6$, and thus contains 1 molecule of hydrochloroplatinic acid, H_2PtCl_6, for each 2 mols. of a monacid or 1 mol. of a diacid base.

The proportion of platinum in the double salt is estimated by ignition, and from this is calculated the total weight of the other constituents associated with one atom of platinum (at. wt. 194.8). By subtracting the weights of six atoms of chlorine and two atoms of hydrogen from the number so obtained, and subsequent division by 2 (for a monacid base), the molecular weight of the base is found.

Under certain conditions the molecular weight of a base may also be determined by estimating the amount of hydrochloric acid in its hydrochloride.

Example I.—Acetic acid on analysis gives the empirical formula CH_2O. It is a monobasic acid, and in silver acetate one hydrogen atom of the acid is therefore replaced by one atom of silver. Hence in order to find the molecular weight of acetic acid we only require to estimate the amount of silver in the silver salt.

0.4120 gm. silver acetate leaves on ignition 0.2665 gm. metallic silver. The salt therefore contains 64.70 per cent. silver; or

100 parts of silver acetate consist of—

Organic residue	= 35.3
Silver	= 64.7

The molecular weight of the organic residue in silver acetate is therefore given by the equation

$$64.7 : 35.3 = 107.88^{[1]} : x$$
$$x = 59$$

Free acetic acid, however, contains in addition to these 59 parts of acetic acid residue a further atom of hydrogen. The molecular weight of the free acid is therefore 60. The simplest formula CH_2O arrived at through analysis, and corresponding to the mol. wt. 30, must accordingly be doubled, and the composition of acetic acid expressed by the formula $C_2H_4O_2$.

This is termed the *molecular formula* and indicates how many atoms of the elements composing the compound are contained in one molecule.

Example II.—Analysis of aniline shows it to consist of 77.42 per cent. C, 7.53 per cent. H, and 15.05 per cent. N; from which is derived the empirical formula C_6H_7N. As is well known, NH_3 combines with HCl to form ammonium chloride in the proportion of 17 : 36.4. Aniline also combines directly with hydrochloric acid to form a similar salt. The molecular weight of aniline may therefore be considered to be that amount which combines with 36.4 gms. HCl, and may be calculated from the chlorine content of aniline hydrochloride. On precipitation with silver nitrate, 0.2590 gm. of this salt gives 0.2870 gm. of silver chloride, which corresponds to 0.073 gm. of HCl. Consequently 0.259 gm. of the salt contains 0.073 gm. of HCl, and by difference 0.186 gm. of aniline. From this it follows from the equation

$$0.073 : 0.186 = 36.4 : x$$

that 93 parts by weight of aniline are united with 36.4 parts of HCl.

The empirical formula C_6H_7N also gives 93 as the molecular weight and is therefore to be considered as the molecular formula of aniline.

Example III.—Caffeine, the physiologically active constituent of coffee and tea, gives on analysis the empirical formula $C_4H_5N_2O$.

It is a monacid base, and its platinum compound consists therefore of 2 mols. of caffeine combined with 2 mols. of hydrochloric acid and 1 mol. of platinum chloride. On ignition 100 parts by weight of this compound give 24.6 parts of metallic platinum; consequently the weight containing one atomic proportion (194.8) of platinum is

$$\frac{194.8 \times 100}{24.6} = 791.8$$

These 791.8 parts of the platinum double salt consist however of 2 mols. of caffeine combined with $2HCl + PtCl_4$; the molecular weight of caffeine is therefore obtained from the equation

$$2x + (2 \times 36.4) + 336.3 = 791.8$$
$$x = 191$$

The formula $C_4H_5N_2O$ quoted above, and corresponding to the mol. wt. 97, must therefore be doubled, giving the molecular formula of caffeine as $C_8H_{10}N_4O_2$.

[1] Atomic weight of silver.

The majority of organic compounds are neither acids nor bases, and with indifferent substances such as these it is frequently impossible to determine the molecular weight by purely chemical methods. Sometimes a detailed study of the reactions of the substance leads to a definite conclusion.

Investigation may be made, for example, as to the manner in which the compound behaves on the substitution of hydrogen by chlorine, and the proportion of the total hydrogen which is replaceable in this way.

Example I.—Chloro substituted carboxylic acids can be prepared by the direct action of chlorine on the acids. Acetic acid, with the empirical formula CH_2O, gives according to experimental conditions three different acids on treatment with chlorine, the final product of substitution having the formula $C_2HCl_3O_2$. In acetic acid itself there are therefore three hydrogen atoms replaceable by chlorine, pointing to the molecular formula $C_2H_4O_2$ for acetic acid.

Example II.—The simplest formula for naphthalene as deduced from analytical data is C_5H_4. Naphthalene reacts with chlorine, however, to give a substance, monochloronaphthalene, containing 73.8 per cent. C, 4.3 per cent. H and 21.9 per cent. Cl, from which the formula $C_{10}H_7Cl$ is derived. This compound is produced from naphthalene by the substitution of hydrogen by chlorine, so that at least one whole atom must have been replaced, since fractions are excluded. From the formula $C_{10}H_7Cl$, therefore, it is obvious that at least $\frac{1}{8}$ of the total hydrogen in the original compound has been replaced, and naphthalene contains in consequence 8, or 2×8, or 3×8, etc., hydrogen atoms, together with 10 (or a multiple of 10) carbon atoms. A multiple of 8 or 10 is, however, out of the question, since no derivatives have ever been obtained from naphthalene indicating the possibility of replacing, for example, $\frac{1}{16}$ or $\frac{1}{24}$ of the total hydrogen. For these reasons the formula C_5H_4 is doubled, and the molecular formula $C_{10}H_8$ assumed for naphthalene.

In some cases an investigation of the additive compounds given with picric acid has been of service in determining the molecular weights of hydrocarbons.[1]

Example III.—An illustration of the manner in which the chemical examination of even more complicated compounds may throw light upon the molecular weight is given in the case of fructose, which has the same percentage composition as acetic acid, and therefore the empirical formula CH_2O. This compound on reduction is converted into mannitol, which may be transformed back to fructose by oxidation. The molecular weight of mannitol is known, since it is a hexahydric alcohol $C_6H_8(OH)_6$, derived from hexane C_6H_{14}, and may be converted into this hydrocarbon. Consequently fructose similarly contains six atoms of carbon and has the molecular formula $C_6H_{12}O_6$.

Determination of Molecular Weight by Physical Methods.[2]

Of the many processes available for this purpose, those which have proved of greatest service to the organic chemist are the determination of vapour density by Victor Meyer's method, and the determinations of

[1] See F. W. Küster, *Ber.*, 1894, 27, 1101.

[2] Two simple micro methods of determining molecular weights have been described by G. Barger (*J. C. S.*, 1904, 85, 286; see also K. Rast, *Ber.*, 1921, 54, 1979) and by K. Rast (*Ber.*, 1922, 55, 1051; also W. S. Sandikow and A. K. Michailow, *Biochem. Zeit.*, 1924, 150, 368; Carlsohn, *Ber.*, 1927, 60, 473).

molecular weight by measuring the elevation of boiling-point or the depression of freezing-point of a solution These are described in full detail in analytical text books

Polymerism

It is seen from the foregoing pages that compounds of the same percentage composition may possess different molecular weights and therefore different properties Such compounds are said to be **polymers** or **polymerides** The number of organic compounds exhibiting this relationship is very large, familiar examples being cyanic acid, $HCNO$, and cyanuric acid, $(HCNO)_3$, formaldehyde, CH_2O, and fructose, $C_6H_{12}O_6$

Interesting cases of polymerism involving very small differences in chemical behaviour will be discussed later under nitroso-compounds

Molecular Structure and Isomerism

Even supposing the composition and molecular weight of a substance to have been determined by means of the methods indicated in the previous chapter, the molecular formula arrived at from these data is not yet sufficiently characteristic to obviate the possibility of confusion with other substances

There are a large number of organic compounds of the same percentage composition and molecular weight which nevertheless differ in their physical and chemical properties Such substances are called **isomers**,[1] or **isomerides**

For example, five different compounds are known having the composition and molecular formula C_3H_6O, and ethylamine and dimethylamine of the same molecular formula C_2H_7N show considerable differences in their chemical and physical behaviour

The reason for such differences must be sought in the internal structure of the molecules, which are assumed to contain a dissimilar *arrangement* of atoms This difference of arrangement may refer —

(*a*) To the manner in which the atoms are linked together, without reference to their positions in space These are cases of **structural isomerism**, and are treated in detail under the theory of structure

(*b*) To the relative position of the atoms in space These are cases of **stereo-isomerism** and are discussed under stereo-chemistry

It is a point of interest that the development of these two branches, which together comprise the theory of molecular structure, originated solely in the sphere of organic chemistry[2]

[1] The term *metamerism*, which was applied to such substances by Berzelius, is less frequently used nowadays and employed only in special cases of isomerism (see p 21) [2] The phenomenon of isomerism is comparatively rare in inorganic chemistry

I.—STRUCTURE

The theory of the structure of organic compounds deals with the manner in which the atoms are connected one with another, and is based on the conception of valency.

(a) Outline of the Theory of Valency

In the year 1858 Kekulé advanced two hypotheses which form the foundation of modern views on the structure of carbon compounds. They postulated that carbon is a tetravalent element and that its atoms have the power to combine one with another.[1] Somewhat later Couper[2] published similar views, which gave rise to the idea of atomic linkings.[3]

Whereas at first it was assumed that the different atoms forming a molecule were held together in such a manner that one attracted all or a certain number of the others, and these themselves exerted a reciprocal attraction on the first, thus holding it in position, it was realised later that this mutual influence extended only from atom to atom. Graphically expressed, the atoms are conceived as strung into a chain, each member being linked to those adjacent to it; if one be removed and not replaced by another, the chain breaks and the compound decomposes. Such chains may be built up from a variety of atoms which need not be of the same valency. A monovalent atom such as hydrogen, however, has only the one opportunity of union, whilst one which is divalent has two, and so on.

The power of union or valency of an atom is indicated by placing small lines or points close to the symbols of the elements, in such a way that each line or point expresses a unit of valency:

H— or H·	—O— (O:)	N with three bonds (N⋮)	—C— with four bonds (C::)
Monovalent	Divalent	Trivalent	Tetravalent

Assuming that in the formation of a compound these valencies are mutually used up, it follows that those elements which combine with hydrogen according to the formula X—H must, like hydrogen, be monovalent. The elements which combine according to the formulæ

$$O{<}^{H}_{H} \qquad N{\lessdot}\begin{matrix}H\\H\\H\end{matrix} \qquad C{\lessdot}\begin{matrix}H\\H\\H\\H\end{matrix}$$

are then di-, tri- and tetravalent respectively.

[1] *Ann.*, 1858, 106, 151. [2] *Ann. chim. phys.*, 1858, (3) 53, 469. [3] It should be noted that Kekulé and Couper are not the actual founders of the theory of valency. This honour belonged to Frankland and Kolbe. The former investigators have, however, rendered the great service of expanding the ideas of Frankland and Kolbe, and of applying them to organic chemistry.

The further development of the theory of valency in inorganic chemistry is complicated by the fact that elements do not always exhibit the same valency, thus copper is mono- or divalent according to whether it is present in a cuprous or a cupric compound In organic chemistry the conditions are simpler, since the elements H, O, and C, of which the majority of important carbon compounds are composed, show with comparatively few exceptions a constant valency In other words, hydrogen is monovalent, oxygen generally divalent [1] and carbon tetravalent

The manner in which the atoms are linked up within the molecule indicates the constitution or structure of the compound, and is expressed by means of constitutional or structural formula These are built up according to the following rules, based on experience —

1 *The carbon atom is usually tetravalent*, in agreement with its position in the periodic classification A carbon atom may thus combine with a maximum of four monovalent atoms or groups This is illustrated by one of the simplest organic compounds, marsh gas or methane, in which one atom of carbon is combined with four atoms of hydrogen

$$\begin{array}{c} H \\ | \\ H-C-H \\ | \\ H \end{array}$$

Methane

In a few compounds such as carbon monoxide, C=O, fulminic acid, HO N=C and others, carbon plays the part of a divalent element It may also exist in the trivalent state in triphenylmethyl,[2] and other compounds

2 *The four valencies of carbon are equivalent to one another*, since the replacement of any one of the four hydrogen atoms in methane by the same monovalent atom, or group of atoms, always yields the same monosubstitution product

Systematic proof of the equivalence of the four carbon valencies has been supplied by Henry,[3] who prepared nitro-methane, $CH_3(NO_2)$, by four different methods, so that the nitro-group each time replaced a different hydrogen atom of methane If these hydrogen atoms are distinguished by the indices *a*, *b*, *c*, and *d*, the compounds prepared may be written as follows,

$$C(NO_2)_aH_bH_cH_d \qquad CH_a(NO_2)_bH_cH_d \qquad CH_aH_b(NO_2)_cH_d$$

and

$$CH_aH_bH_c(NO_2)_d,$$

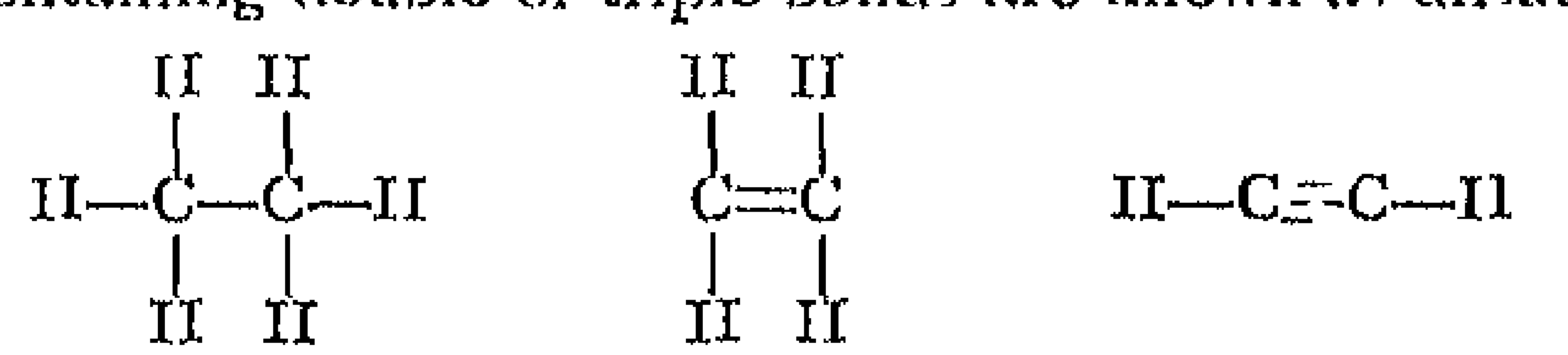
all of which proved to be identical

[1] It should be borne in mind that oxygen in organic compounds may under special conditions be tetravalent (see Collie and Tickle, *J C S*, 1899, 75, 710, and Baeyer and Villiger, *Ber*, 1901, 34, 2685) and carbon possibly trivalent. [2] The divalency of carbon has been discussed by Nef, *Ann*, 270, 280, 287, 298, 309, 310, 318 Trivalent carbon has been assumed by M. Gomberg, Gomberg and Schoepfle, *J Am. C S*, 1917, 39, 1652 For the views of Nef on valency see *J Am C S.*, 1904, 26, 1549. [3] *C. r.*, 1887, 104, 1106, *Z. phys Ch*, 1888, 2, 553, *C.*, 1907, 1, 1312

For this purpose Henry started from methyl iodide, $CI_aH_bH_cH_d$, in which iodine may be assumed to occupy the position *a*, and converted it directly into *a* nitromethane, $C(NO_2)_aH_bH_cH_d$, by means of silver nitrite. Another portion of methyl iodide was heated with potassium cyanide, yielding methyl cyanide which on hydrolysis gave acetic acid, also having the carboxyl group in the *a* position. This on chlorination gave mono-chloroacetic acid, which may be written $C(COOH)_aCl_bH_cH_d$. The latter was readily changed into *b* nitroacetic acid and finally to *b* nitromethane, $CH_a(NO_2)_bH_cH_d$. Another part of the chloroacetic acid was converted into malonic acid, chlorinated to $C(COOH)_a(COOH)_bCl_cH_d$, and after treatment with silver nitrite was subsequently converted into the third nitromethane, $CH_aH_b(NO_2)_cH_d$. Yet another introduction of a carboxyl group, followed by chlorination and nitration, gave the fourth nitromethane, $CH_aH_bH_c(NO_2)_d$. As already mentioned, the four nitromethanes obtained in this way proved to be identical.

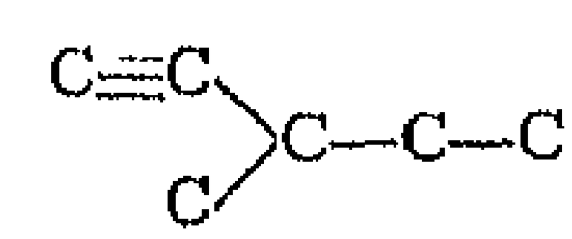
3. *Carbon atoms have a great capacity for combining with one another.* Recognition of this fact was of the greatest importance for the development of structural chemistry, since it led directly to the possibility of writing constitutional formulæ for carbon compounds. In the union of carbon atoms it is supposed that each atom is bound by a valency, or several valencies, to a neighbouring atom; the remaining valencies can then be saturated by hydrogen, or other simple or complex groups. Two carbon atoms may thus be linked together with one, two, or three valencies, these being termed single, double, or triple bonds respectively, C—C, C=C, C≡C.

Those substances in which, as in I, only singly bound carbon atoms occur, are called saturated carbon compounds, whereas those, as in II and III, containing double or triple bonds are known as unsaturated.

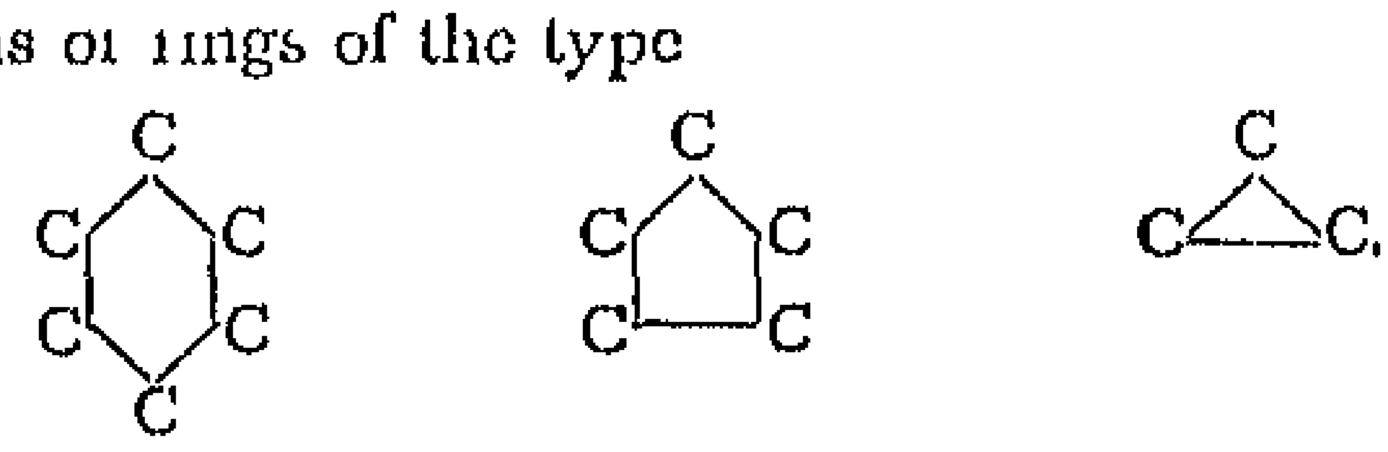


I. Ethane II. Ethylene III. Acetylene

In a similar way it is possible for three, four, or any larger number of carbon atoms to combine together. The final product may be an open chain such as

C—C—C—C C—C—C=C—C—C 

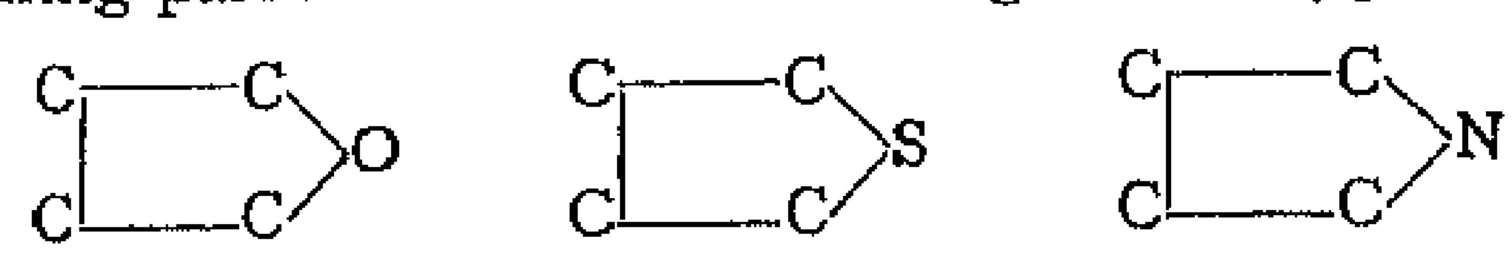
or closed chains or rings of the type



A number of important open chain carbon compounds are found in animal and vegetable fats. Consequently that section of organic chemistry which treats of open chain compounds is known as the fatty

series, and a substance belonging to this class as a *fatty* or *aliphatic compound*

On the other hand, those containing closed chains come under the heading of *cyclic compounds* If the rings consist entirely of carbon atoms, as in the above examples, they are termed *carbocyclic*, if in addition to carbon we have elements such as oxygen, sulphur or nitrogen, taking part in the formation of rings of the type

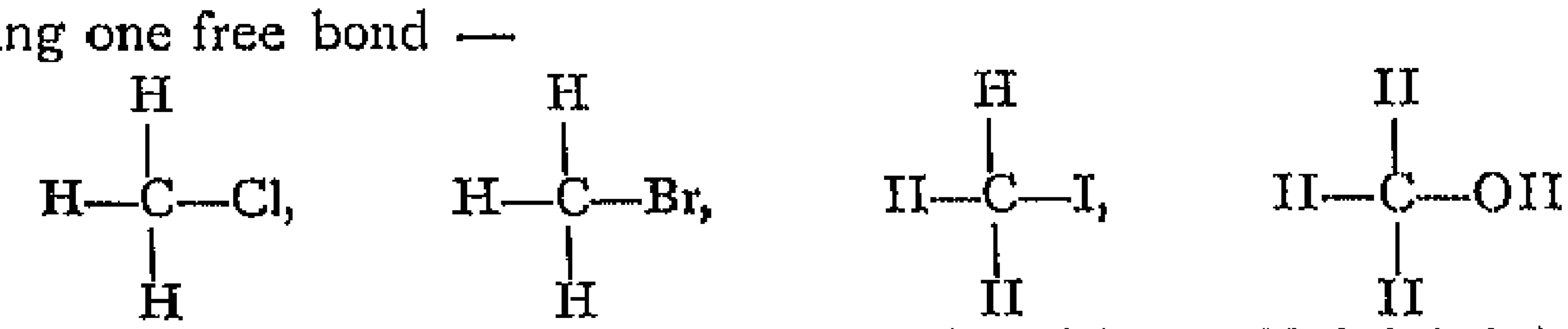


the compounds are termed *heterocyclic*

Among the carbocyclic rings, the one containing six carbon atoms with six free valencies possesses a special interest From it are derived substances classed as *aromatic compounds* or *benzene derivatives*

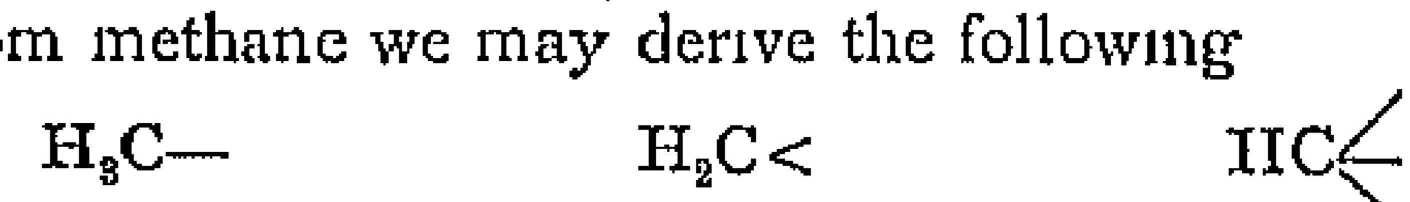
(*b*) Substitution, Radicals, Isomerism.

Under suitable conditions the elements in organic compounds may be replaced, or substituted, in equivalent proportions by other elements Once again considering the simplest compound of carbon, methane, it is possible for one of its hydrogen atoms to be replaced by one atom of chlorine, bromine or iodine, or by a group of atoms, such as OH, having one free bond —



Methyl chloride | Methyl bromide | Methyl iodide | Methyl alcohol

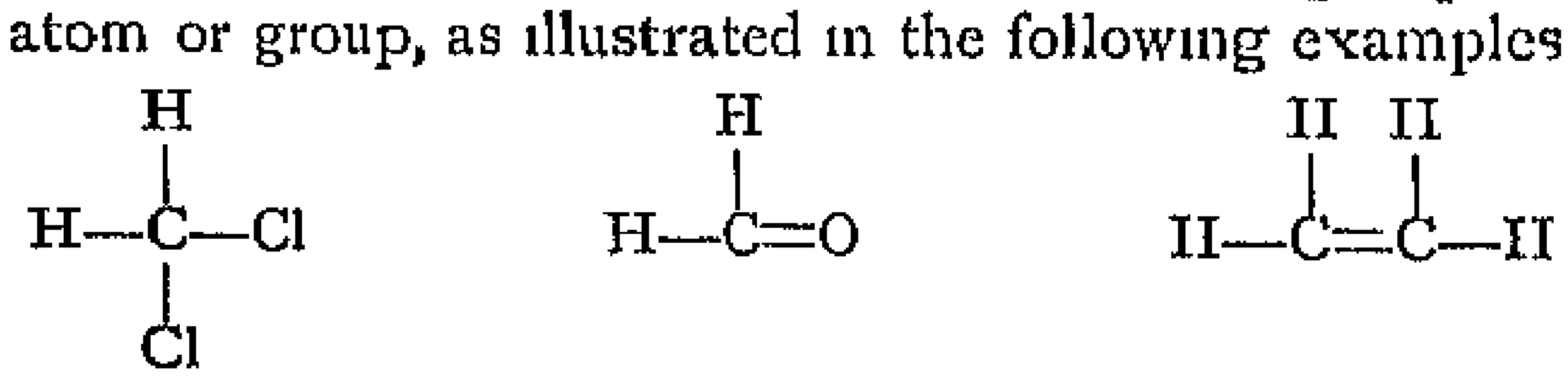
Such groups of atoms, which still exhibit free affinity and therefore do not exist in the free state, are often transferable as such from one compound to another, and are termed **radicals** or groups The group OH is known as the hydroxyl radical, and since it possesses only one free affinity is monovalent By the removal of successive atoms of hydrogen from methane we may derive the following



Methyl | Methylene | Methenyl or methine

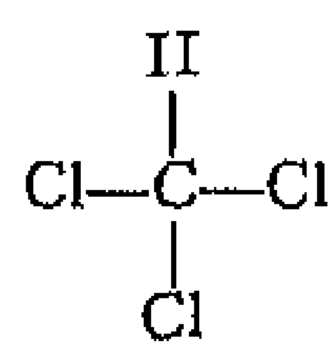
which are mono , di- and trivalent radicals respectively

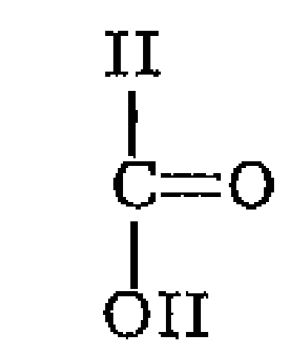
In the same way it is easy to understand that two atoms of hydrogen may be replaced either by two monovalent atoms or groups, or by one divalent atom or group, as illustrated in the following examples



Methylene chloride | Formaldehyde | Ethylene

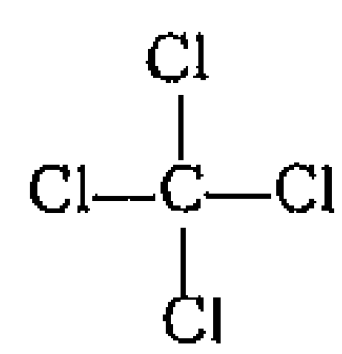
Similarly three hydrogen atoms of methane may be substituted by three monovalent atoms or radicals, by one monovalent and one divalent atom (or radical), or by a trivalent atom (or radical), as in the following compounds

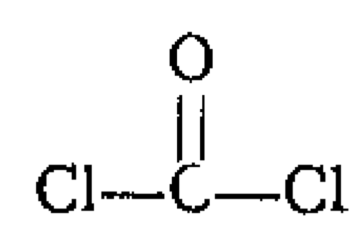

Chloroform

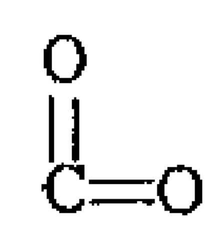

Formic acid

$HC \equiv CH$
Acetylene

Finally all four hydrogen atoms may be replaced by four monovalent atoms or radicals, etc, as in—


Carbon tetrachloride

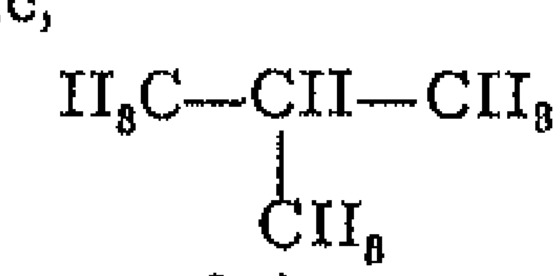

Phosgene


Carbon dioxide

The substitution of hydrogen in methane by the radical CH_3 will be considered in more detail When an atom of hydrogen in CH_4 is exchanged for the monovalent radical CH_3, the hydrocarbon ethane, $H_3C—CH_3$, is produced If now in this compound H is again replaced by CH_3, we obtain $CH_3—CH_2—CH_3$, propane Obviously there is only ethane or propane possible, since it is immaterial which hydrogen atom in methane or ethane is substituted If, however, a hydrogen atom in propane is once again exchanged for CH_3, two isomeric compounds may be formed, according to whether the H replaced is situated in one of the two CH_3 groups or in the CH_2 In the first case normal butane is obtained

$$H_3C—CH_2—CH_2—CH_3$$
Normal butane

and in the second isobutane,


Isobutane

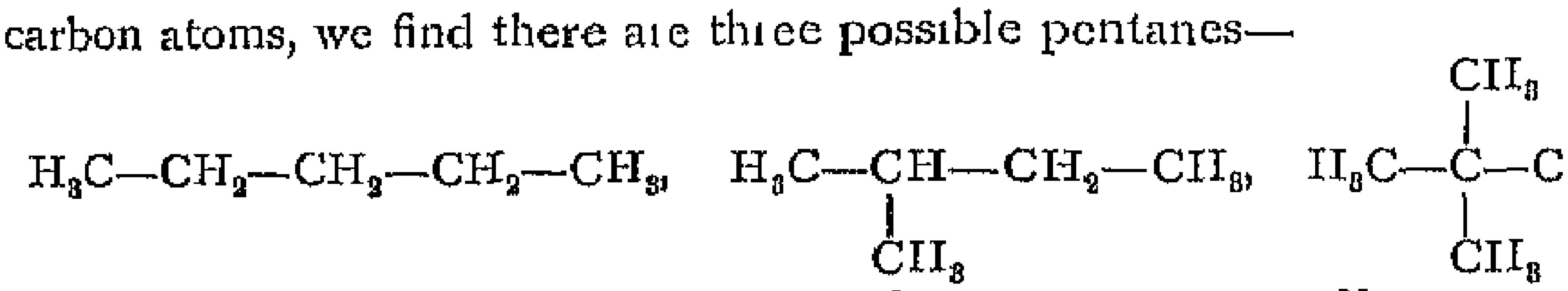
both of the composition C_4H_{10}

As in numerous other cases, the cause of isomerism in the butanes is the different constitution of the carbon chains Normal butane contains a straight carbon chain, whereas isobutane has a branched chain

Isomerism of this type involving a different structure, or manner of linking, of the carbon chain or nucleus is termed **chain or nuclear isomerism**

It is seen from the foregoing that there are two ways of linking up four carbon atoms, and if in a similar manner we derive from the

formulæ of the two butanes the corresponding compounds with f
carbon atoms, we find there are three possible pentanes—



Normal pentane Isopentane Neopentane o
tetramethyl meth

With an increasing number of carbon atoms, the number of differ modes of linking, and therefore the possible number of isomers, increa with extraordinary rapidity There are five hexanes, C_6H_{14}, ni heptanes, C_7H_{16}, and eighteen octanes, C_8H_{18}, theoretically possible

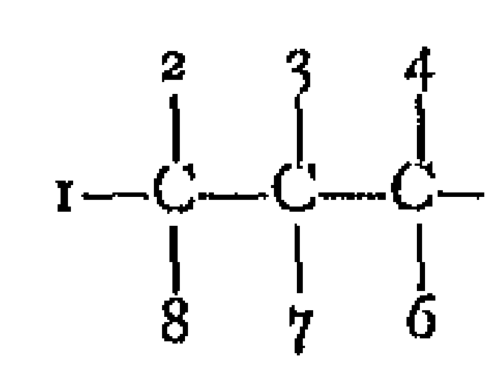
It is also possible for hydrogen atoms in all these hydrocarbons be replaced by other elements or radicals This gives rise to a differe kind of isomerism from that discussed above For example, differe chlorine compounds may be derived from propane, $CH_3\ CH_2\ CH$ according as the halogen replaces hydrogen in the CH_2 or one of t CH_3 groups—

$H_3C—CH_2—CH_2Cl$ and $H_3C—CHCl—CH_3$
Normal propyl chloride Isopropyl chloride

The reason for the difference between these two compounds is n longer to be found in the different structure of their carbon chains, b in the different position of the chlorine atom in the same carbon cha

Isomerism caused by the different position of substituents in t same carbon chain is termed **position isomerism.**

This can lead to conditions of great complexity, particularly when the carbon framework is saturated with different monovalent atoms or groups It is thus theoretically possible to form over one hundred different derivatives of propane, C_3H_8, if in the annexed formula the numbers 1 to 8 represent different monovale atoms



(c) Homologues, Metamerism

If we compare the formulæ of the simple hydrocarbons derived fro methane by substitution, as described in the previous section,

CH_4	C_2H_6	C_3H_8	C_4H_{10}
Methane	Ethane	Propane	Butane,

we observe at once that each member of the series differs in its com position by CH_2 from the following member Indicating the numb of carbon atoms in these hydrocarbons by n, where n may be any whol number from 1 upwards, the number of hydrogen atoms is given b $2n+2$, and the series possesses the common formula C_nH_{2n+2}

In all these hydrocarbons we may replace the hydrogen atom by other atoms or radicals On substituting a hydrogen atom in th

above four hydrocarbons by a hydroxyl group, we obtain, irrespective of possible isomerides, the following compounds

$CH_3 \cdot OH$	$C_2H_5 \cdot OH$	$C_3H_7 \cdot OH$	$C_4H_9 \cdot OH$
Methyl alcohol	Ethyl alcohol	Propyl alcohol	Butyl alcohol

In this series also, each member differs from the next by CH_2, and all are expressed by the general formula $C_nH_{2n+1} \cdot OH$

Substitution by the most varied elements or radicals always results in the formation of groups of bodies whose members differ from one to another by CH_2

A group of similarly constituted compounds of this type is termed a **homologous series**, and its individual members **homologues** It is easily understood that compounds which differ merely in the replacement of H by CH_3, and are otherwise of similar structure, possess for the most part the same chemical properties Thus the hydrocarbons CH_4, C_2H_6, C_3H_8, C_4H_{10}, show great similarity in chemical behaviour, and the same is true of the hydroxyl compounds, CH_3OH, C_2H_5OH, C_3H_7OH, C_4H_9OH Many other such series are met with in organic chemistry, and in consequence the study of the subject is very much lightened

It has been shown by Kopp that in a homologous series the physical properties of the compounds change gradually from member to member (p 78)

The expression **metamerism**, which is seldom employed nowadays, refers to that kind of isomerism involving radicals attached to a polyvalent element Numerous examples of this kind are known, of which the following will serve as illustrations —

General Formula			
	Butylamine		Ethyl dimethylamine
$C_4H_{11}N$	$\left.\begin{matrix}C_4H_9\\H\\H\end{matrix}\right\}N$		$\left.\begin{matrix}C_2H_5\\CH_3\\CH_3\end{matrix}\right\}N$
	Dipropyl ether	Methyl-pentyl ether	Ethyl-butyl ether
$C_6H_{14}O$	$\left.\begin{matrix}C_3H_7\\C_3H_7\end{matrix}\right\}O$	$\left.\begin{matrix}CH_3\\C_5H_{11}\end{matrix}\right\}O$	$\left.\begin{matrix}C_2H_5\\C_4H_9\end{matrix}\right\}O$
	Butyric acid	Methyl-propionate	Ethyl acetate
$C_4H_8O_2$	$\left.\begin{matrix}C_3H_7O\\H\end{matrix}\right\}O$	$\left.\begin{matrix}CH_3\\C_3H_5O\end{matrix}\right\}O$	$\left.\begin{matrix}C_2H_5\\C_2H_3O\end{matrix}\right\}O$

(*d*) Constitution of Unsaturated Carbon Compounds

Many instances of unsaturated compounds are known in organic chemistry, and these have for long been a fruitful subject of investigation Earlier work in this direction led to the assumption of double and triple bonds, as illustrated in the formulæ—

$H_2C{=}CH_2$	$HC{\equiv}CH$
Ethylene	Acetylene

A number of unsaturated carbon compounds are also known in which the presence of a divalent carbon atom is assumed,[1] as in

C O	C S	C NH	C NOH
Carbon monoxide	Carbon monosulphide	Hydrogen cyanide	Fulminic acid

Nevertheless, it should be noted that this hypothesis of multiple bonds is not indispensable for the explanation of unsaturated compounds, although it is still accepted by the great majority of chemists despite the objections that have been brought against it

The theory of the existence of double and multiple bonds arose from the observation that all those reactions which would be expected to yield methylene, CH_2, invariably lead to the formation of its homologue, ethylene, C_2H_4 It was therefore assumed that free valencies could not exist on the carbon atom, and consequently of the two formulæ proposed for ethylene, $H_2C = CH_2$ and $H_3C - CH =$, Erlenmeyer decided in favour of the first

The most characteristic property of unsaturated compounds is their ability to add on elements or radicals and pass into saturated compounds,[2] for example—

$$\underset{\text{Ethylene}}{H_2C\ \ CH_2} + H_2 = \underset{\text{Ethane}}{H_3C\ \ CH_3}$$

Doubly bound carbon atoms appear therefore to be less firmly united than singly bound atoms, whereas the reverse might have been expected Baeyer attempted to explain this peculiarity by his *strain theory*[3]

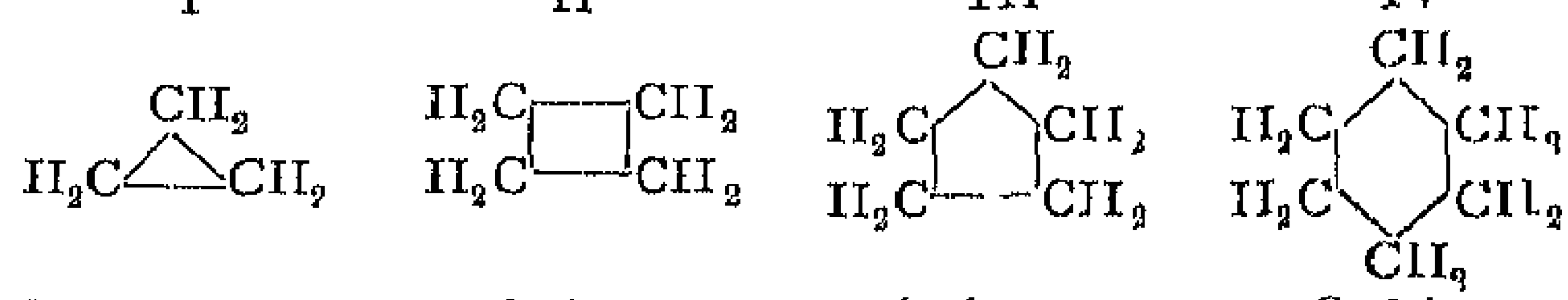
From stereo chemical considerations Baeyer came to the conclusion that the angle between the valencies of the carbon atom, according to the tetrahedral model (see p 32), remain unaltered when two carbon atoms are united by a single bond, but before a double bond can come into being, the respective valencies must be displaced from their original direction by a certain angle A definite strain is thus set up in the molecule, rendering the multiple bond easily ruptured by suitable reagents to form a compound with single bonds and normally directed valencies A similar, but even greater strain may be imagined to exist in compounds containing triple bonds As was pointed out by Baeyer, the internal strain in the case of the polyacetylenes tends to manifest itself in the development of explosive properties

In the same manner the distortion of the carbon bonds may be calculated for various cyclic compounds It is found that this is comparatively large in cyclopropane (I), becomes less in cyclobutane (II) and disappears almost entirely in cyclopentane (III) In cyclohexane (IV) the displacement from the normal is somewhat greater than in the 5 membered compound In qualitative agreement with Baeyer's strain theory it is found that the stability of the ring structure towards

[1] *Cf* p 16 [2] Reference should be made to Vorländer's explanation of the mechanism of addition reactions, *Ann*, 1905, **341**, 1, 1906, **345**, 155 [3] See p 319 for a fuller discussion

reagents increases as we pass from cyclopropane to cyclopentane, which is the most stable of the lower members of the series (see also p 349 *et seq*)

I II III IV



Cyclopropane Cyclobutane Cyclopentane Cyclohexane

Later, a detailed study of unsaturated compounds led to the conclusion that the double bond did not completely utilise the affinity between the two carbon atoms, but left a surplus on each atom which was termed *residual affinity* These ideas, as developed by Thiele, have aroused great interest and discussion

Thiele's theory of unsaturated compounds was originally put forward to explain the observation of Baeyer and Rupe, that when muconic acid is reduced the first step is the addition of two hydrogen atoms to the extreme ends of the hydrocarbon chain, with the formation of a new double bond in the centre On further reduction this double

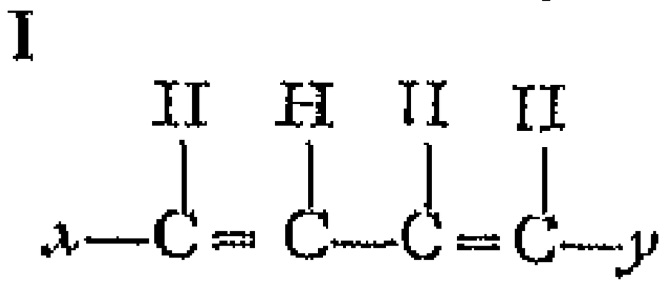
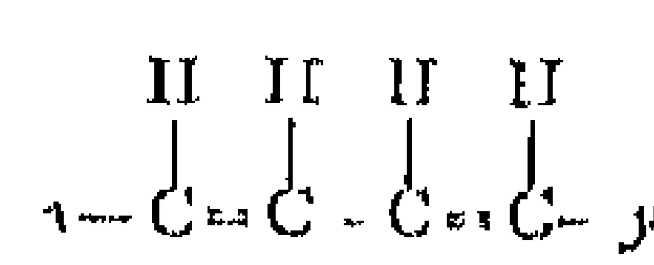
$$\underset{\text{Muconic acid}}{HOOC—CH=CH—CH=CH—COOH} \rightarrow \underset{\text{Dihydromuconic acid}}{HOOC—CH_2—CH=CH—CH_2—COOH}$$

bond is also attacked Similar displacements have been noted by Baeyer[1] in the reduction of benzene carboxylic acids

Thiele assumed that all such unsaturated compounds contain one or more double bonds, but that the two affinities of a double bond do not completely saturate one another, leaving a certain residual affinity or *partial valency* in excess on each carbon atom This is illustrated graphically in the following formula, where the dotted lines indicate partial valencies Addition to this compound follows by each new atom first attaching itself to a partial valency, subsequently taking up the full valency with the simultaneous disappearance of the double bond

$$\begin{matrix}x\\y\end{matrix}>C=C<\begin{matrix}u\\z\end{matrix} + H_2 \longrightarrow \begin{matrix}x\\y\end{matrix}>\underset{H}{C}=\underset{H}{C}<\begin{matrix}u\\z\end{matrix} \longrightarrow \begin{matrix}x\\y\end{matrix}>\underset{H}{\overset{}{C}}—\underset{H}{C}<\begin{matrix}u\\z\end{matrix}$$

It is supposed that in a system of alternating single and double bonds such as I

I  II 

1 2 3 4

which Thiele describes as *conjugated double bonds*, the two central partial valencies mutually saturate one another, so that addition must first occur at the ends of the system, in the 1, 4 positions (II)

[1] Baeyer, *Ann*, 1889, 251, 271

This may be made clearer by comparing a pair of conjugated double bonds to a magnet, the activity of which is manifested only at the poles When it is divided in half two new magnets are produced, and on forming it into a closed ring all characteristic activity is lost, to be regenerated in its original strength on again opening the ring As will be explained later, this theory furnishes a particularly good representation of the nature of the benzene ring

Thiele illustrated the use of his hypothesis by a large number of examples, and it appears to give a satisfactory explanation of the behaviour of many unsaturated organic compounds In recent years, however, facts have come to light which are not in entire agreement with the rule of 1 4 addition Thorpe and his co-workers[1] have re-examined the behaviour of butadiene towards bromine and have confirmed the simultaneous formation of two primary dibromo addition products, one of which is a 1 2- and the other a 1 4-compound Either of these compounds, on being heated, undergoes rearrangement to give a mixture of the two isomerides containing about 80 per cent of the 1 4 compound, although the isomeric change is very slow at room temperature Hence the process of addition to such a system is not as simple as is represented in Thiele's theory

$$CH_2\ CH\ CH\ CH_2 \longrightarrow \left\{ \begin{array}{l} (BrCH_2\ CHBr\ .\ CH\ CH_2) \\ \qquad\qquad \uparrow\downarrow \\ BrCH_2\ CH\ CH\ CH_2Br \end{array} \right.$$

In a similar manner isoprene, $CH_2\ C(CH_3)\ CH\ CH_2$, adds on hydrogen in the presence of platinum black to give in the first instance a mixture of 1 2, 1 4 and 3 4 derivatives,[2] these three reactions proceeding simultaneously The unsaturated cyclic compounds 1 3-cyclohexadiene and 1 3-cyclopentadiene also yield considerable proportions of 1 2-dibromo addition products[3]

Other theories on the constitution of unsaturated carbon compounds have been put forward from time to time by different investigators,[4] but up to the present none has obtained any general support

A further contribution to the valency problem has been developed in modern times by Werner, who, unlike Thiele, makes no assumption of directed valency bonds, but substitutes the conception of affinity distributed over definite areas of the atomic surface[5] According to these views, which have been most fruitful in their application to complex inorganic compounds, the valency of a carbon atom varies with the spatial configuration of the atom and its degree of affinity

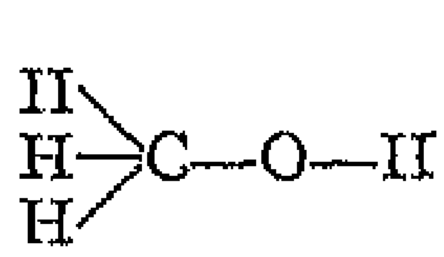
[1] E H Farmer, C D Lawrence and J F Thorpe, *J C S*, 1928, 729 See also Straus, *Ber*, 1909, 42, 2872. [2] S V Lebedev and A O Yakubchik, *J C S*, 1929, 823 [3] Farmer and Scott, *J C S*, 1929, 172 [4] Erlenmeyer, *Ann*, 1901, 316, 43, *J pr Ch*, 1902 (2), 65, 346 Vorlander, *Ann*, 1902, 320, 66 F W Hinrichsen, *Z phys Ch*, 1902, 39, 301, *Ber*, 1904, 37, 1121, *Ann*, 1904, 336, 168 [5] A Werner, *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie* (1923)

towards adjacent atoms. Compounds of the "first order" are thus built up in which the individual atoms still contain surplus components of affinity, even if the substance is of the type known as saturated. This residual valency can attach other atoms or molecules to form compounds of the "second order" (*e.g.*, molecular compounds). But whether we prefer the idea of fixed valency, which has already proved of incalculable value in organic problems, or the conceptions of Werner as developed in the chemistry of the metalloids, the assumption of residual affinity remains indispensable.

(e) Derivation of Structural or Constitutional Formulæ

The constitutional or structural formula is derived from the molecular formula by building up every possible combination of the constituent atoms, consistent with the foregoing considerations of valency, and selecting that particular one which agrees best with the properties of the compound.

It is a comparatively simple matter to assign a formula where the number of atoms in the molecule is small. Thus a compound of molecular formula CH_4O must possess the structure given below, if we assume the valencies of C, O and H to be four, two and one respectively. In other cases it may be necessary to make a choice from several alternatives.



The final allocation of a structural formula should be made with reference to the following general considerations, based on laboratory experience:—

1. The possibility of converting the substance into, or of forming it from, compounds of known constitution. In this connection it may be noted that *when compounds undergo double decomposition, the new atom or radical entering into a molecule usually takes up the position occupied by the out-going atom or radical*.[1] The structure of the radicals exchanged generally remains unaltered during this process.

For example, ethyl chloride, C_2H_5Cl, for which there is only one possible constitution, is under certain conditions transformed into alcohol, C_2H_6O, by interaction with water:

$$C_2H_5Cl + H_2O = C_2H_5OH + HCl.$$

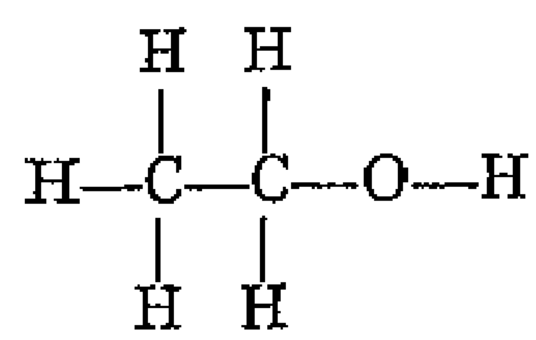
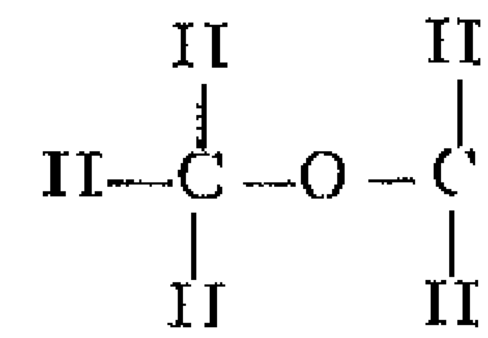
Conversely, ethyl alcohol by treatment with hydrochloric acid regenerates ethyl chloride:

$$C_2H_5OH + HCl = C_2H_5Cl + H_2O.$$

We must therefore assume alcohol to contain the radical C_2H_5- or $H_3.CH_2-$, already known to exist in ethyl chloride, and consequently

[1] Only in special cases, to be discussed later, does a "wandering" of atoms or radicals take place. See, for example, the Walden Inversion (p. 278).

also the monovalent hydroxyl group $-OH$ For these reasons alcohol is allotted formula I below,

I  II 

which is in complete harmony with its chemical behaviour Of the six hydrogen atoms present, one obviously differs from the other five in its reactivity and the ease with which it is replaced by metals or radicals Hence this hydrogen atom is assumed to be linked indirectly to carbon through oxygen

Consideration of these facts leads to the rejection of the only other possible structure II for a substance of molecular formula C_2H_6O The latter represents methyl ether, which is isomeric with ethyl alcohol Here the six hydrogen atoms are all seen to be in the same state of combination Formula II may also be derived from the formation of methyl ether by the interaction of sodium methoxide and methyl iodide

$$H_3C\ O\ Na + I\ CH_3 = H_3C\ O\ CH_3 + NaI$$

As a further example, the constitution of acetic acid, $C_2H_4O_2$, may be examined This substance is produced by the oxidation of ethyl alcohol, according to the equation

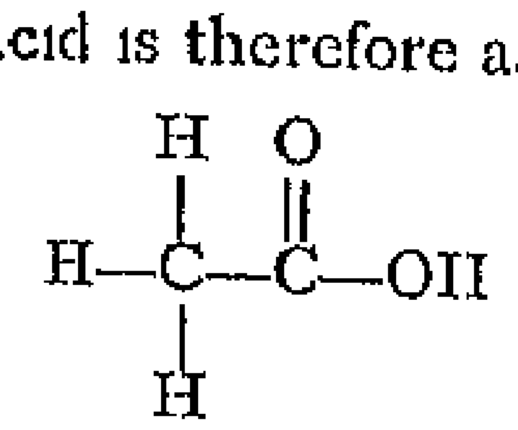
$$C_2H_6O + O_2 = C_2H_4O_2 + H_2O$$

One of the four hydrogen atoms differs in its properties from the other three It is readily replaced by metals or monovalent radicals and its whole behaviour shows it to be united to oxygen in the form of a hydroxyl group, and not directly attached to carbon

The first step was therefore to write acetic acid as $C_2H_3O(OH)$, and next to determine the structure of the C_2H_3O radical This problem was solved by Kekulé, who showed that the three hydrogens must be attached to one and the same carbon atom, since potassium acetate, when heated with potassium hydroxide, yields methane and potassium carbonate

$$\underset{\text{Potassium acetate}}{C_2H_3O(OK)} + KOH = \underset{\text{Methane}}{CH_4} + K_2CO_3$$

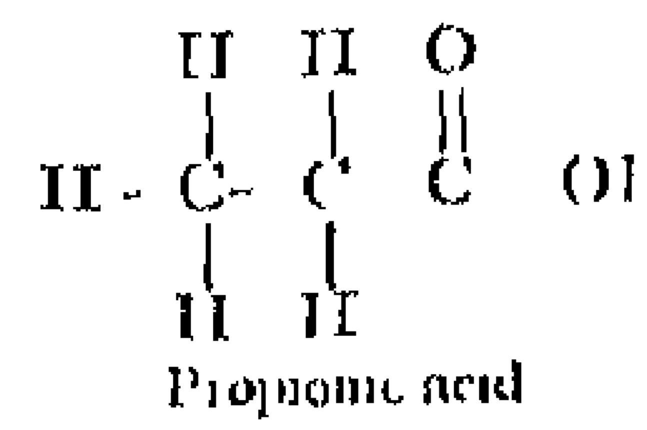
The constitution of acetic acid is therefore assumed to be



It will be seen when we come to deal with the properties of the acid that this formula is in good agreement with its chemical behaviour

2 *The chemical and physical character of a compound is a function of its molecular structure*, and the chemical similarity of a number of

compounds is dependent on the common presence of certain "typical" groups of atoms. Constitution is therefore frequently decided by comparing the physical or chemical properties of the substance with those of a compound of known structure. Every alcohol, for example, contains the hydroxyl group (—OH), and all compounds which show those properties characteristic of the alcohols may also be assumed to contain a hydroxyl group in the molecule.



Propionic acid

The large majority of organic acids contain the carboxyl group, —COOH, as given above under acetic acid. If then primary propyl alcohol, $CH_3 \cdot CH_2 \cdot CH_2 \cdot OH$, yields on oxidation an acid of the molecular formula $C_3H_6O_2$, the latter probably contains the group —COOH and possesses the structural formula given above.

Intramolecular Rearrangement

As already indicated, the atom or radical entering a molecule by double decomposition occasionally fails to occupy the position of the out-going atom or radical, more particularly if the reaction takes place at a high temperature.

Hence some uncertainty attaches to a constitutional formula deduced by any single one of the methods described under I. The result can only be regarded as probable when derived from the consideration of several different reactions, each of which leads to the same conclusion.

In general, a structural formula is only accepted as established beyond doubt when it has been confirmed by synthesis.

The Electronic Theory of Valency.[1]

Great advances have been made in our conception of valency by interpreting it in the light of the electronic theory, according to which atoms are built up solely of ***protons*** and ***electrons***. A ***proton*** is a unit of positive electricity having extremely small dimensions and a mass of 1·007 (O = 16). An ***electron***, or unit of negative electricity, is of considerably greater dimensions than a proton but only about 1/1840 of its mass. Atoms, then, being externally neutral bodies, are composed of equal numbers of protons and electrons. All of the protons, with about half of the electrons, are packed closely together into a small space constituting the atomic ***nucleus***. The remainder of the electrons, the number of which gives the ***atomic number*** of the atom, are in rapid rotation in orbits around the nucleus and hence occupy a much greater volume than the latter. These planetary electrons arrange themselves in layers round the nucleus, each layer containing a definite

[1] For detailed treatment see G. N. Lewis on *Valence*, Sidgwick, *The Electronic Theory of Valency* (Churchill, 1927).

number corresponding to the condition of maximum electrical stability The chemist, however, is concerned almost exclusively with the outermost layer, since the chemical properties of the atom, including that of valency, depend almost entirely on the number and disposition of the electrons in the *outer shell*, which is therefore termed the *valency shell*

Except for the transition elements in group 8 and the rare gases in group O, the number of electrons in the valency shell corresponds to the number of the group into which the element falls in the periodic scheme Thus hydrogen and the alkali metals, Na,K, etc, in the first group have only one valency electron, carbon in the fourth group has four, nitrogen has five, oxygen six, and chlorine seven In the rare gases, from neon upwards, there is a complete outer group of eight electrons These atoms can be represented diagrammatically as follows —

H Na C N O Cl Ne

Chemical reactions are supposed to occur owing to the tendency of valency shells to assume a more stable arrangement For the majority of the common elements stability is reached when there is an outer shell of eight electrons (an *octet*), for hydrogen and the rare gas helium, however, the stable number is two In the case of elements of groups I and II, possessing one and two valency electrons respectively, the stable condition may be attained by the complete loss of these electrons This change occurs on ionization and results in the exposure of the underlying shell of electrons, which is already in its most stable arrangement Elements of group VII, on the other hand, may readily complete their octets by gaining or even sharing an electron from another atom In the rare gases the valency shell exists in a formation of maximum stability, hence these elements have no chemical reactivity whatever

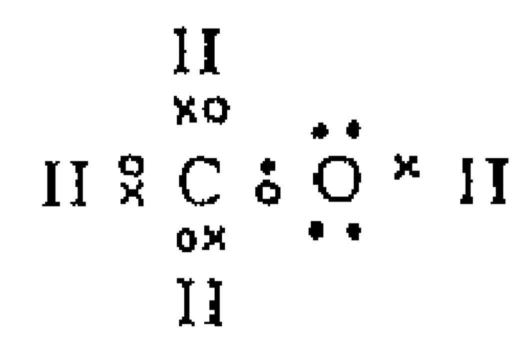
Actual combination between two atoms may be supposed to occur in one of two ways, both of which were suggested by Lewis

1 Union may take place by an atom completely transferring one or more of its electrons to another atom As atoms are externally neutral groups of protons and electrons, this leaves the first atom positively and the second negatively charged Combination of this type is found chiefly among salts of acids and bases, and is known as **electro-valency** The oppositely charged ions may be regarded as separate entities, normally held together by electrostatic attraction The equation given below illustrates the electronic changes which take place when sodium and chlorine combine to give sodium chloride In order to make these and the following formulæ clearer, the electrons belonging to different atoms are in some cases indicated by different signs

$$\underset{\text{Sodium}}{\mathrm{Na}} + \underset{\text{Chlorine}}{\mathrm{Cl}} \longrightarrow \underset{\text{Sodium chloride}}{\overset{+}{\mathrm{Na}}\quad\overset{-}{\mathrm{Cl}}}$$

2. A type of valency which is of much more frequent occurrence in organic compounds is that of **co-valency**. In this case the two atoms unite by holding a pair of electrons in common, one being contributed by each atom. For example, the oxygen atom in water has increased its sextet to an octet by acquiring a share in two other valency electrons from the atoms to which it is linked. At the same time each hydrogen atom has attained a stable shell of two by sharing an oxygen electron. In methyl alcohol the four electrons in the outer shell of the carbon atom are raised to eight by sharing with three hydrogen electrons and one oxygen electron. Each pair of shared electrons constitutes a non-ionizing bond as commonly pictured in organic formulæ. For simplicity of representation the electrons are figured as static, but it must

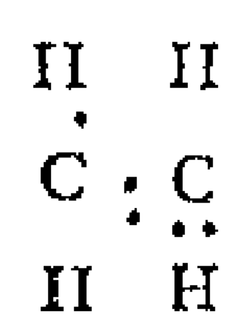
Water



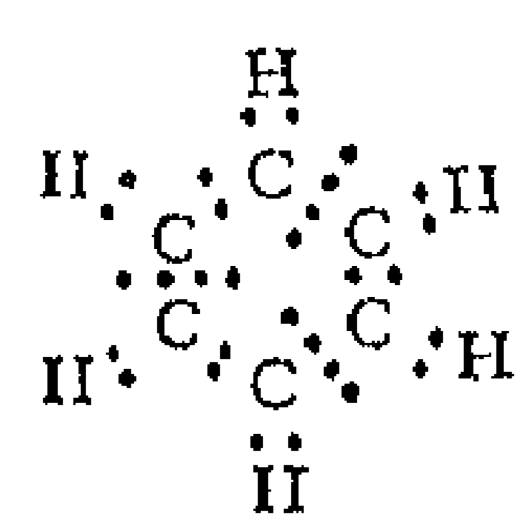
Methyl alcohol

be remembered that they are in reality supposed to be in a state of rapid motion.

The ordinary *double bond*, as in C=C or C=O, is regarded as a double co-valency, *i.e.* as four electrons shared between two atoms, two electrons being supplied by each. A double bond of this type is symmetrical in structure, and has a plane of symmetry containing the double linking.



Ethylene



Benzene.[1]

3. Another and more recently proposed form of co-valency,[2] the development of which is chiefly due to Lowry and to Sidgwick, is that in which *one* of the atoms supplies *both* of the electrons required for the union. Lowry and Sugden term this type of bond a *semi-polar double bond* (see below), Sidgwick refers to it as a *co-ordinate link*,[3] because he has shown it to be present in the co-ordination compounds investigated by Werner. This mode of union was first applied to certain inorganic compounds by Lewis.

In order that combination of this kind may be possible, one of the atoms (the *donor*) must have at least two valency electrons (termed

[1] For an alternative formula see p. 356. [2] A singlet or 1 electron link may also be possible in certain cases, *cf.* Sugden, *The Parachor and Valency*, p. 129 (Routledge, 1930). [3] Sidgwick, *J. C. S.*, 1923, 123, 725.

a *lone pair*) which are not concerned in union with any other part of the molecule, and the other atom (the *acceptor*) must be able to take up two electrons to form a more stable arrangement.[1] Many atoms, even when in the combined state, possess one or more of these lone pairs of electrons. Oxygen in water has two and nitrogen in ammonia or organic bases has one. Under suitable conditions, therefore, O and N in these compounds may function as *donor atoms*. Atomic oxygen, on the other hand, has a valency shell of six electrons (two less than the stable arrangement) and may play the part of an *acceptor atom*. Thus in trimethylamine oxide, $(CH_3)_3NO$, the two nitrogen electrons which were unattached in trimethylamine are supposed to be shared with the oxygen. Sidgwick represents this kind of linking by a short arrow, *e.g.* N→O. The single line indicates that it is a link formed by the sharing of two electrons, and the direction of the arrow shows that both the electrons are provided by the nitrogen atom.

$$
\begin{array}{c} H \\ \overset{\times\cdot}{} \\ H{\times}\ddot{N}{:}H \\ \cdot \end{array}
\qquad\qquad
\begin{array}{c} CH_3 \\ CH_3{:}\underset{\times\cdot}{\overset{\cdot\times}{N}}{\cdot}\underset{\circ\circ}{\overset{\circ\circ}{O}}{\circ\circ} \\ CH_3 \end{array}
\quad \text{or} \quad
\begin{array}{ccc} & CH_3 & \\ & | & \\ CH_3 & N & \rightarrow O \\ & | & \\ & CH_3 & \end{array}
$$

Ammonia — Trimethylamine oxide

An arrangement such as this necessarily implies that the molecule has developed polarity. The nitrogen atom becomes positively charged owing to two of its electrons being less in its proximity than previous to the union, and the oxygen atom becomes negatively charged, having two additional electrons in its outer shell. Lowry, who first proposed the above electronic formula for the amine oxides,[2] describes the linking between N and O as a **semi-polar double bond**, since it may be regarded as being composed of a normal co-valence together with an electro-valence. This is expressed in the adjoining formula, in which the upper bond indicates a co-valence (two shared electrons, one from each atom) and the lower half arrow represents an electro valence, an electron having been completely transferred from N to O. The net result is the same as before. The oxygen atom, previously having a shell of six electrons, has now gained a part share in two more, supplied in effect by the nitrogen atom. The electronic formula is thus the same as that given above.

$$
\begin{array}{ccc} & CH_3 & \\ & | & \\ CH_3 & N & \rightleftharpoons O \\ & | & \\ & CH_3 & \end{array}
$$

If the older formulation of the amine oxides, $(CH_3)_3N = O$, which assumes the presence of a normal double bond, is translated into the electronic formula, the nitrogen atom must be represented as having a valency shell of ten electrons. Such an arrangement is unstable. The new formulation, on the other hand, preserves the octet, which is the stable arrangement for nitrogen.

$$
\underset{\cdot\times}{\overset{\times\cdot}{:N}}\,\vdots\,\underset{\circ\circ}{\overset{\circ\circ}{O}}
$$

[1] Sidgwick, *The Electronic Theory of Valency*, p. 116. [2] Lowry, *Trans. Faraday Soc.*, 1923, 18, 285.

According to modern views, the union between N and O in the amine oxides does not possess the properties of an ordinary double bond, although until recently it was always written as such. As will be seen later the new formulation has since been justified not only on stereo-chemical grounds (p 61) but also by the evidence of Sugden's parachor (p 81). Sugden has shown that most of the double bonds commonly encountered in organic formulæ are true double co-valencies, but that the nitro group, $—NO_2$, only appears to possess one true double bond, together with one semi-polar double bond (or co-ordinate link). Nitrobenzene should therefore be written as $C_6H_5—N\genfrac{}{}{0pt}{}{\nearrow O}{\searrow O}$

A peculiarity of the co-ordinate link, according to Sidgwick, is that it is not subject to the numerical limits of valency typical of the periodic group to which the element belongs.[1] In this it differs from the electrovalent bonds.

Although co-ordinate links occur less frequently in organic compounds than simple co-valent links, they appear to be responsible for the formation of co-ordination compounds and for many cases of molecular association.

From the foregoing pages it will be seen that the usual formulæ of the organic chemist are readily translated into electronic formulæ by replacing each single non-ionizing bond by a pair of shared electrons, each ionizing bond by the transfer of an electron, and each double bond by four shared electrons, except in cases where a co-ordinate link or semi-polar double bond has been shown to be present.

II.—STEREO-CHEMISTRY [2]

Whereas the theory of structure treats only of the sequence and manner in which the atoms are linked together within the molecule, stereo-chemistry concerns itself with those chemical phenomena which are directly attributable to the configuration, or disposition of the atoms in space. That type of isomerism which involves substances of the same constitution, but different configuration, is called **stereo-isomerism**, and the substances are known as *stereo-isomerides*.

From the historical point of view, stereo-chemistry has developed logically from the theory of structure. At first it was found possible to explain the number and properties of almost all compounds of similar molecular formula by assuming a difference of constitution. One by

[1] Hydrogen, for example, may under certain conditions exhibit a valency of two. See also Lowry and Burgess, *J C S*, 1923, 123, 2111. [2] See A W Stewart, *Stereo-chemistry* (Longmans); Hantzsch, *Grundriss der Stereochemie*, 2nd edition, Leipzig, 1904; Werner, *Lehrbuch der Stereochemie*, Jena, 1904; P Walden, *Fünfzig Jahre Stereochemischer Lehre und Forschung*, Ber, 1925, 58, 237; G Wittig, *Stereochemie* (1930).

one, however, cases of isomerism were discovered which could not be explained on the ground of structural dissimilarity, and these were for a time classed as "physically isomeric substances," without any reason being assigned for the isomerism.

Stimulated by the work of Pasteur and Wislicenus,[1] a stereo-chemical theory of the isomerism of optically active compounds was developed independently and almost simultaneously in 1874 by Van't Hoff[2] and Le Bel. Since then many investigators have made valuable contributions to this subject and none more so than Emil Fischer, in his brilliant researches on the sugars.

The stereo chemistry of nitrogen has similarly been advanced by the work of Hantzsch and Werner, Le Bel, Pope and Peachy, Wedekind, Mills and others.

1. Stereo chemistry of Carbon

According to their behaviour the stereo-isomeric carbon compounds may be divided into two groups as follows:—

A. Substances which are identical in all their chief properties, but differ in their "optical activity" or action on polarised light, when examined in the fused state or in solution. Such compounds are termed **optical isomerides, optical antipodes** or **enantiomorphs**, and with few exceptions contain within the molecule at least one *asymmetric carbon atom* (*cf.* footnote 1, p. 35). By this term is understood a carbon atom whose four valencies are united to four *different* monovalent atoms or groups.

B. Substances which, having the same structural formula, differ in all their physical and many of their chemical properties, but exert no influence on polarised light. These are compounds containing double or triple bonds, and are generally described shortly as **geometrical isomerides**. Many of the saturated cyclic compounds also exhibit this kind of isomerism. (See cyclohexane series, p. 461.)

In their original publications Van't Hoff and Le Bel showed that both of these types of isomerism could be explained on the assumption that the valency bonds were arranged in three dimensions around the carbon atom.

A. Optical Isomerism

According to Van't Hoff's fundamental hypothesis of stereo-chemistry, the four valency bonds of the carbon atom are imagined to be directed towards the summits of a regular tetrahedron, at the centre of which lies the atom itself. It is easily seen by reference to figures 3 and 4[3]

[1] Wislicenus, *Ann.* 1873, 167, 343. [2] Van't Hoff, *The Arrangement of Atoms in Space*, translated by A. Eiloart (Longmans). [3] For the sake of clearness the carbon atom, which is supposed to lie at the centre of the tetrahedron with its bonds directed towards *a*, *b*, *c* and *d*, is omitted in the space formulae. The letters *a*, *b*, *c*, *d*, represent the four different atoms or radicals attached to the asymmetric atom.

that a substance of the type C*abcd*, in which *a*, *b*, *c* and *d* are four different atoms or groups, can assume two different configurations which are not superimposable. A carbon atom such as this is described as asymmetric.

One configuration is a mirror-image of the other, and the difference between them is comparable with that existing between the right hand and the left. This *enantiomorphism* or mirror-image relationship of the molecules is repeated in the optical and crystallographic properties of the substances; but in most remaining physical and chemical properties the compounds are identical. Structural figures such as 3 and 4, expressing the spatial arrangement of the atoms, are called space formulæ, and illustrate the fact that *the molecule of an optically active compound possesses no plane of symmetry.*

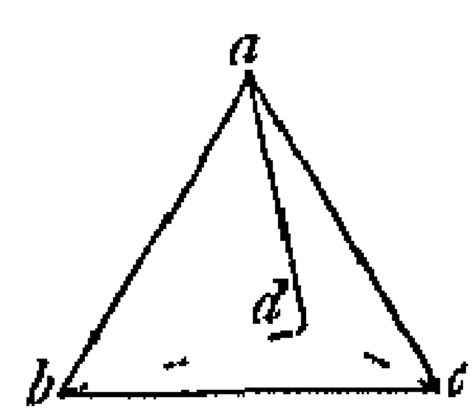


FIG. 3

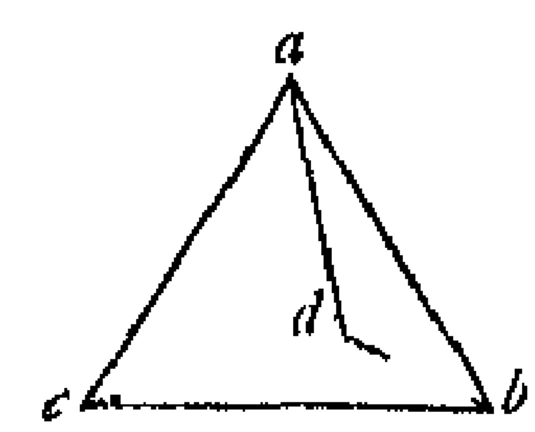


FIG. 4

In studying stereo chemical problems it is advisable not only to visualise the space formulæ indirectly on the plane of the paper, but also directly by use of space models as devised by Kekulé, Van't Hoff and others. The simplest type of model is that in which the four valency bonds are represented by four pieces of rubber tubing, connected together at one end, and directed towards the corners of a regular tetrahedron. Coloured balls attached to the tubes by rods represent the different groups.

Van't Hoff's theory of the carbon atom is supported by Bragg's X-ray analysis of the structure of the diamond,[1] in which the carbon atoms are found to be united by tetrahedrally directed valency bonds.

In its main essentials Le Bel's theory agrees with that of Van't Hoff. Le Bel, however, makes no assumption regarding the geometrical arrangement of the valency bonds in space. He states that molecular asymmetry will necessarily exist if the four different radicals are arranged in space around the carbon atom, whatever may be the geometrical form of the molecule. In this respect Van't Hoff's ideas accord more closely with later developments of stereo-chemistry.

Certain inorganic substances (*e.g.* sodium chlorate) are optically active in the crystalline state. This is due to the *molecules* being arranged in an asymmetric manner within the crystal and the activity therefore disappears when the crystal passes into solution. The optical activity of carbon and other compounds in solution is a consequence of the asymmetric arrangement of the *atoms* in the molecule. In some cases the crystals of such compounds also possess optical activity.

[1] W. H. Bragg, *Proc. Roy. Soc.*, 1913, 89 A, 277.

Compounds containing one Asymmetric Carbon Atom

As already indicated, the most striking difference between isomers containing an asymmetric carbon atom lies in their optical activity in the liquid or dissolved state. To every active compound rotating the plane of polarisation through a certain angle in a given direction, there corresponds an isomeride which, otherwise identical in properties, rotates the plane of polarised light to the same extent in the opposite direction.

The two enantiomorphs differ only in sign of rotation, and are therefore termed *optical antipodes*. They are distinguished arbitrarily as dextrorotatory and laevorotatory modifications, or more commonly by prefixing the letters *d* and *l*- (or + and −) to the name of the substance, *e.g.*, *d*- and *l*-lactic acids.

If equimolecular quantities of the *d*- and *l*-forms of a compound are mixed with one another, a product is produced in which all optical activity disappears, owing to the mutual or *external compensation* of the two constituents. Inactive products of this type are called *racemic compounds* or *mixtures*[1] and are usually distinguished by the prefix *r*- or *dl*-. When crystalline they are frequently definite compounds having double the molecular weight of the *d*- or *l*-forms. In the fluid state or in solution racemic compounds exist as a mixture of the *r*-form in equilibrium with equivalent amounts of the *d*- and *l*-modifications, thus recalling the behaviour of double salts.[2] By methods to be described later it is possible to resolve these racemic compounds into their active components.

A few rare cases have been observed, notably in the camphor series, in which no definite compound is produced, but the two optical enantiomorphs form mixed crystals with one another, the product being termed a *pseudoracemic mixture*.[3]

A typical instance of a compound containing an asymmetric carbon atom is lactic acid, $H_3C \cdot CH(OH) \cdot COOH$, which occurs in two optically

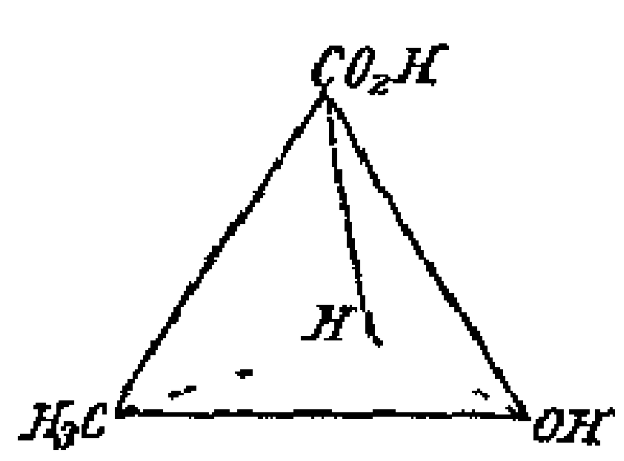


FIG. 5

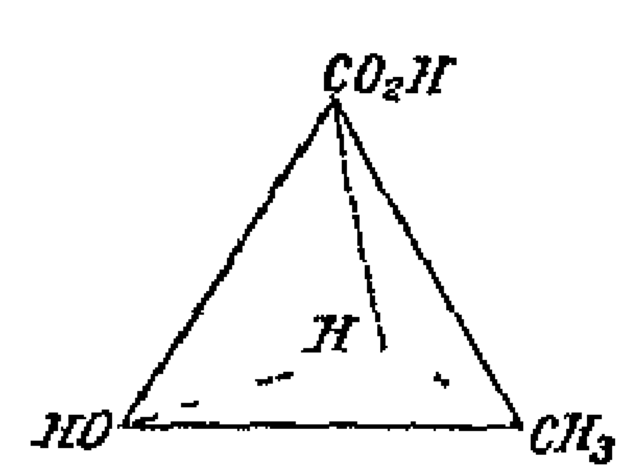


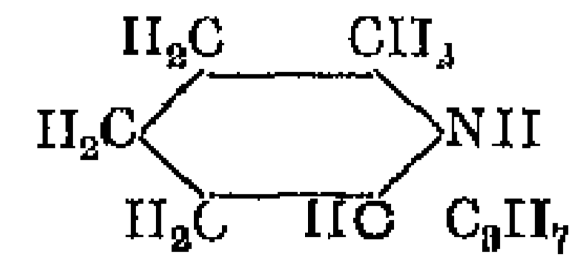
FIG. 6

active modifications and an optically inactive or racemic form. The two optical antipodes are related to one another in the manner shown in Figs. 5 and 6.

[1] The name is derived from racemic acid, the first representative of this class to be observed.
[2] Racemic compounds are not necessarily *completely* dissociated into the *d*- and *l* forms in solution. Cotton has shown that on mixing equimolecular solutions of copper *d* and *l* tartrates, dissolved in alkali, the colour at once deepens, thus indicating compound formation (*Ann. Chim. Phys.*, 1896, 8, 347; *Trans. Faraday Soc.*, 1930, 377).   [3] See Pope and Read, *J. C. S.*, 1913, 103, 1515.

The following additional examples may be mentioned, in which the asymmetric atom is indicated by heavier type

Malic acid, $COOH \cdot \mathbf{C}H(OH) \cdot CH_2 \cdot COOH$
Asparagine, $COOH \cdot \mathbf{C}H(NH_2) \cdot CH_2 \cdot CONH_2$
Mandelic acid, $C_6H_5 \cdot \mathbf{C}H(OH) \cdot COOH$
Chloro-bromo-fluoro-acetic acid, $(ClBrF)\mathbf{C} \cdot COOH$

Coniine, 

Each of these compounds is known in two optically active forms and an inactive racemic form

It can readily be demonstrated that the existence of these isomerides, like the property of optical activity itself, is dependent on molecular asymmetry With the destruction of the asymmetry of the carbon atom—for example, when a molecule of the formula $C\,a\,b\,c\,d$ is converted into $C\,a\,b\,c_2$—both optical activity and isomerism disappear[1] Thus the reduction of either of the optically active malic acids, $HOOC \cdot CH_2 \cdot CH(OH) \cdot COOH$, leads to the formation of the same inactive succinic acid, $HOOC \cdot CH_2 \cdot CH_2 \cdot COOH$

Compounds with two or more Asymmetric Carbon Atoms

As the number of asymmetric carbon atoms in a compound becomes greater, the number of possible isomerides increases rapidly *In general, a compound of unsymmetrical structure containing* n *asymmetric carbon atoms can exist in* 2^n *isomerides*, made up of a number of pairs of mirror-image forms possessing equal and opposite rotations This general statement postulates a structural dissimilarity between the asymmetric atoms involved, if this is not the case, and the molecule is symmetrically built, certain of the asymmetric atoms will be structurally alike and consequently some of the possibilities of isomerism will vanish

It is only feasible at this stage to discuss the isomerism dependent on the presence of two asymmetric atoms within the molecule Examples of greater complexity, such as those offered in the sugar series, will be examined later under their respective headings

As already stated above, compounds containing two dissimilar asymmetric carbon atoms are capable of existing in 2^2, or four, optical isomerides, made up of two pairs possessing equal and opposite rotatory power, to these must be added the two (inactive) racemic forms This can be deduced in a simple manner by distinguishing the two atoms by the letters A and B, and then different spatial

[1] Those compounds which contain asymmetric carbon atoms form, in some respects, a special class of substances in which the spatial arrangement of the atoms within the molecule is such that no plane of symmetry is present Such compounds must occur in two modifications, the space formulæ of which are mirror images of one another. As Pasteur first recognised they are distinguished by enantiomorphous crystal structure and optical activity of contrary sign

configurations by the signs + and − We have then the following active compounds

1	2	3	4
+ A	− A	+ A	− A
+ B	− B	− B	+ B

An example of this type is dibromo-cinnamic acid,

$$C_6H_5 \cdot CHBr—CHBr \cdot COOH,$$

which is known to occur in four active as well as two racemic forms

Compounds possessing two asymmetric but structurally similar carbon atoms, of the general formula $C_{abc}—C_{abc}$, exist in three different configurations, two of which are optically active antipodes, the other is represented by an internally compensated structure and cannot be resolved into active components (see p 39) In addition, the two active enantiomorphs may unite to produce a racemic form

The different modifications can be derived in a manner similar to that shown above, by placing A = B, in which case configurations 3 and 4 become identical

1	2	3
+ A	− A	+ A
+ A	− A	− A

The substance represented by 3 is optically inactive, despite the presence of two asymmetric complexes, owing to the activity of the one group being equal and opposite to that of the other In other words, it is *internally compensated* Compounds of this type are also described as *i*- or *meso*- forms This inactive and non-resolvable form cannot occur in cases where there is only one asymmetric atom present

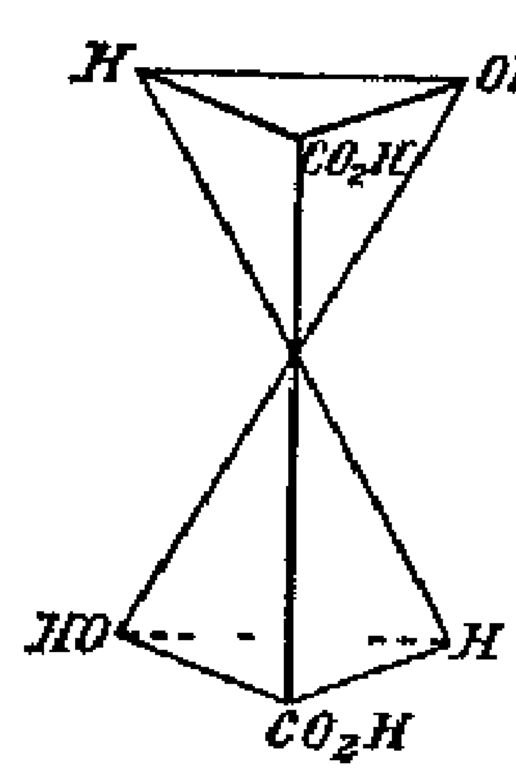


FIG 7

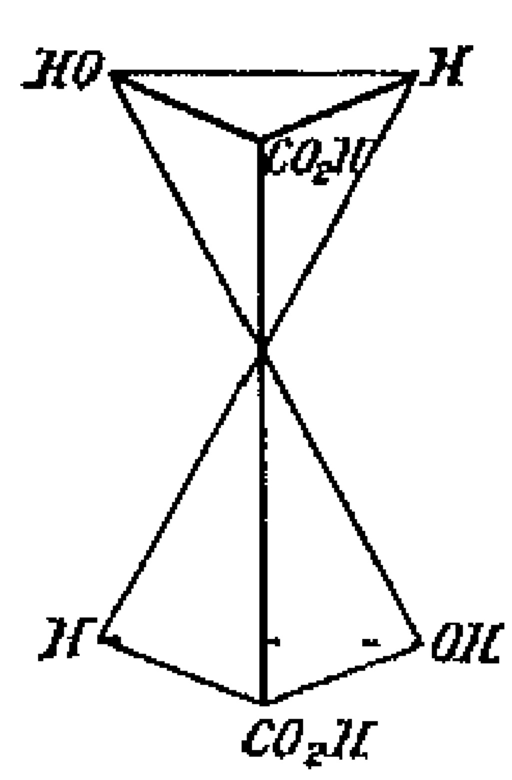


FIG 8

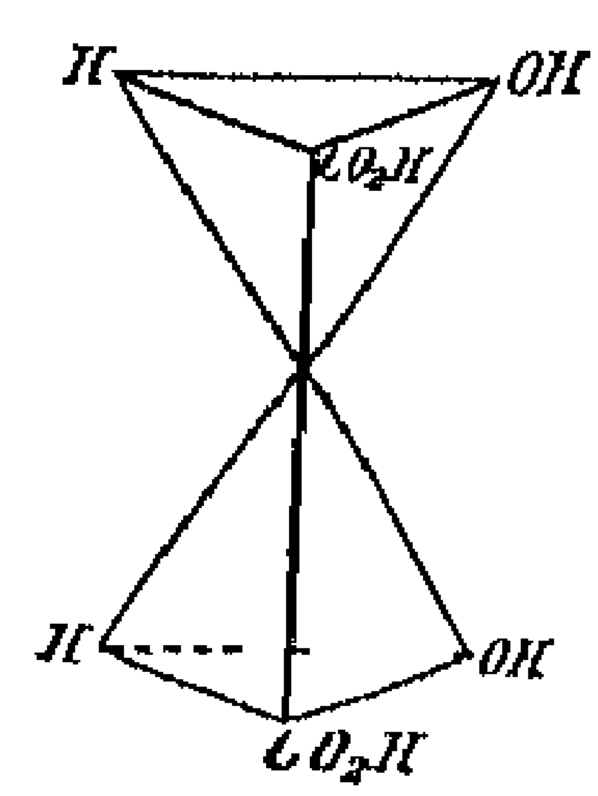
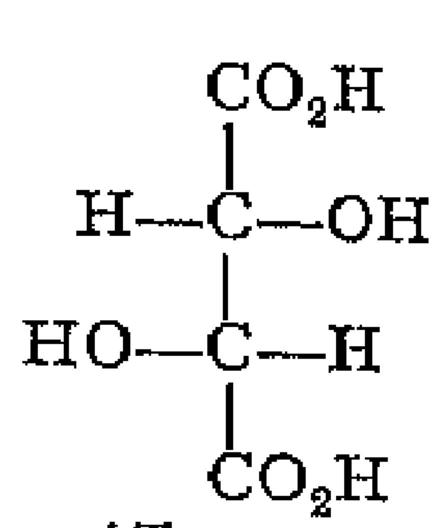
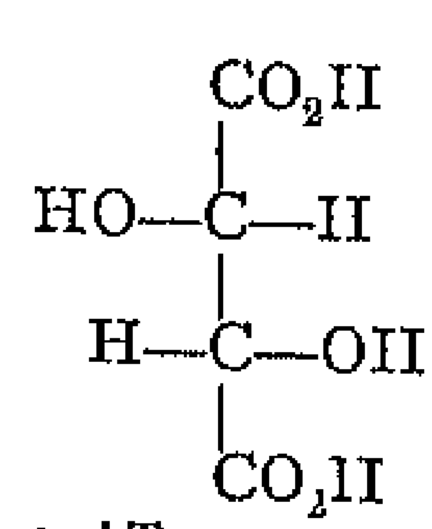


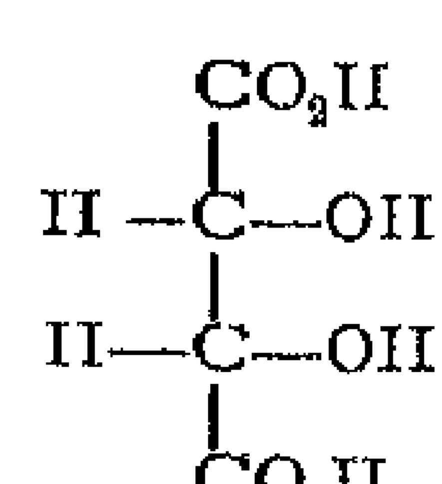
FIG 9



1 *d*-Tartaric acid



2 *l* Tartaric acid



3 *i* Tartaric acid or meso-tartaric acid

4 *dl* Tartaric acid, *i* tartaric or racemic acid

in the molecule, and is to be distinguished carefully from the inactive, *externally compensated*, racemic type which by special methods can be resolved or separated into its optically active components

One of the best known examples of isomeric compounds containing two similar asymmetric atoms is found in the dihydroxy-succinic acids, HOOC CHOH CHOH COOH, which have played a conspicuous part in the history of optical activity In accordance with theory, these exist as dextro , laevo-, and *i*- or meso-tartaric acids, and in addition as racemic acid, which has double the molecular weight of the above three forms, and is produced by union of *d*- and *l*-tartaric acids The dextro- and laevo-acids are optical antipodes, whereas meso-tartaric and racemic acids are inactive As shown in the formulæ at bottom of previous page, racemic acid is resolvable and meso-tartaric acid non-resolvable The lack of optical activity in meso-tartaric acid is also revealed by the fact that the molecular formula (see Fig 9) possesses a *plane of symmetry*, i e, a plane dividing the structure into two halves bearing the relationship of object to mirror-image

Racemisation

It should be noted that many optically active compounds become more or less completely inactive under the influence of heat or chemical reagents, a process known as *racemisation* In this way *d*-tartaric acid when heated with water is transformed into a mixture of racemic and meso-tartaric acids

A number of other acids such as aspartic, mandelic and camphoric acids may be converted into their racemic forms in a similar way Some compounds (limonene, pinene, amyl alcohol) lose their activity on being merely heated to a sufficiently high temperature, others (tartaric acid, mandelic acid, amyl alcohol and many amino acids) are readily racemised when heated with aqueous alkalis, in still other cases (limonene, *d*-valeric acid) sulphuric acid is an active catalyst

In a few instances the optical activity has been found to disappear spontaneously in the course of time at the ordinary temperature Walden discovered that esters of optically active bromo-succinic and phenyl-bromacetic acids gradually become inactive during the lapse of several years This is known as *auto-racemisation* It has recently been shown, however, that no racemisation occurs in these esters if they are completely freed from traces of hydrobromic acid [1]

Racemisation appears to be due to the occurrence of some kind of molecular change under the influence of heat or a suitable catalyst, as the result of which an asymmetric molecule A exists temporarily in equilibrium with an isomeric form B (or a simple derivative thereof) which is not asymmetric in structure The optically active (say, *d*-rotatory) compound A is therefore undergoing constant conversion

[1] R Kuhn and T. Wagner-Jauregg, *Naturwissenschaft*, 1929, 17, 103

into the inactive substance B The molecules of A regenerated from B by the equilibrium process will, however, be composed of an equal mixture of *d*- and *l*-rotatory forms, since in general there is no reason [illegible]

$$\underset{\text{Asymmetric (active)}}{d\text{A}} \longrightarrow \underset{\text{Symmetrical (inactive)}}{\text{B}} \begin{matrix} \nearrow d\text{A} \\ \searrow l\text{A} \end{matrix} \Big\} \underset{\text{Racemic (inactive)}}{dl\text{A}}$$

why one mirror-image isomeride should be produced in excess of the other In the end, therefore, the whole of the active form A is converted into the racemic compound *dl*-A

One of the best investigated cases of racemisation is that of optically active acids in the presence of alkalis It was suggested by [illegible] (*Brit Assoc Rep*, 1904, p 211) that the racemisation of mandelic acid under this treatment took place according to the scheme

$$\underset{\text{Active form}}{C_6H_5{-}CHOH{-}C{\lesssim}^{O}_{OH}} \longrightarrow \underset{\text{Intermediate symmetrical form}}{\left[C_6H_5{-}C(OH){=}C{\lesssim}^{OH}_{OH}\right]} \longrightarrow \underset{\text{[illegible]}}{C_6H_5{-}CHOH{-}[illegible]}$$

This particular mechanism can be applied to all acids in which the asymmetric atom has a hydrogen atom attached to it and occupies the *a*-position to the carboxyl group The asymmetry of the molecule is then destroyed by the hydrogen atom migrating to the ketonic oxygen as in the unstable intermediate phase In agreement with this hypothesis, McKenzie[1] has shown that phenyl-*p*-tolyl acetic acid $\genfrac{}{}{0pt}{}{C_6H_5}{CH_3\cdot C_6H_4}{>}CH{-}COOH$ is readily racemised by alkalis, but that atrolactic acid, $\genfrac{}{}{0pt}{}{C_6H_5}{CH_3}{>}C(OH){-}COOH$, which has no labile hydrogen atom attached to the asymmetric C-atom, remains unaffected A somewhat different example is that of *β*-phenyl butyric acid, $\genfrac{}{}{0pt}{}{C_6H_5}{CH_3}{>}CH{-}CH_2{-}COOH$, which is able to undergo the above tautomeric change, but since the asymmetric atom is here in the *β* position the change does not destroy the asymmetry This acid does not lose its activity when heated with alkalis The interconversion of acids of the sugar series (*epimerisation*) when heated with quinoline is a racemisation process affecting the *a* carbon atom, and may be explained in the same manner (see p 292)

McKenzie, however, points out that the direct union of a phenyl group to the asymmetric atom is a second factor making for ease of

[1] A McKenzie, *J C S*, 1915, 107, 704, 1919, 115, 602, Wren, *ibid*, 1918, 113, 210

racemisation in acids of the above type.[1] The replacement of the phenyl group by an alkyl or even by a benzyl radical stabilises the molecule towards alcoholic potash. Thus the following acids are not racemised by this reagent, although they contain in the α-position an asymmetric atom attached to hydrogen:

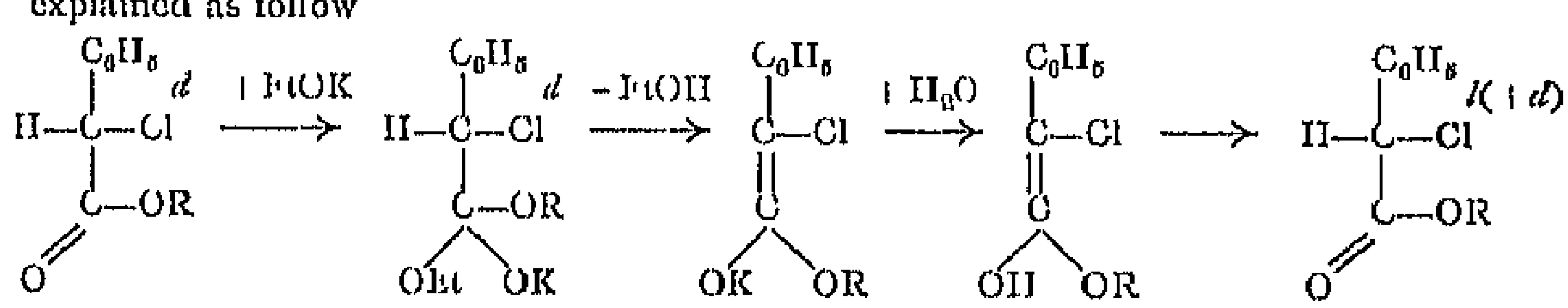
$$\begin{array}{c} OH \\ C_6H_5\cdot CH_2\cdot C\cdot COOH \\ H \end{array} \qquad \begin{array}{c} OH \\ CH_3\cdot C\cdot COOH \\ H \end{array}$$

β-Phenyl-lactic acid. Lactic acid.

Similar considerations may be applied to other classes of optically active compounds. Secondary aliphatic alcohols of the formula R·CHOH·R, for example, in which there is no possibility of a tautomeric change of the above type, are known to be stable to alkalis,[2] whereas active benzoin readily loses its rotatory power. In the latter compound inactivation may occur by the following process:

$$\underset{\text{Asymmetric}}{C_6H_5\cdot CHOH\cdot CO\cdot C_6H_5} \rightleftarrows \underset{\text{Symmetrical}}{C_6H_5\cdot C(OH){=}C(OH)\cdot C_6H_5}$$

In the case of esters composed of an optically active acid combined with an active alcohol the process of racemisation may lead to a curious result. McKenzie[1] has shown that when *l*-menthyl *d*-phenylchloroacetate is treated with a few drops of alcoholic alkali (insufficient to produce complete hydrolysis) a mixture is obtained containing *l*-menthyl *l*-phenylchloracetate and *l*-menthyl *d*-phenylchloracetate, having the former in excess. This is termed *asymmetric catalytic racemisation*, and is explained as follow:



In the last two stages the presence of the optically active group R brings about an asymmetric synthesis (see p. 46) giving an excess of the *l*-acid structure.

Resolution of Racemic Compounds

Compounds containing asymmetric carbon atoms, which have been prepared synthetically by methods not involving the use of any active substance, are never found to possess optical activity. They generally conform to the racemic type, since in such a synthesis there are always produced equimolecular amounts of the dextro- and laevo-rotatory forms. On the other hand, asymmetric compounds produced with the mediation of living organisms are almost invariably active.[3]

[1] A. McKenzie and Miss I. A. Smith, *Ber.*, 1925, 58, 894. [2] Pickard and Kenyon, *J. C. S.*, 1911, 99, 62. [3] Further information concerning the ability of vegetable organisms to effect direct syntheses of optically active compounds will be found in a paper by E. Fischer, *Ber.*, 1894, 27, 2031. If a chemical synthesis is effected with the intermediate aid of an optically active substance which is subsequently removed, the product may on occasion also exhibit activity. By means of such *asymmetric syntheses* (p. 46), it is possible to imitate the processes of the living agency.

Notwithstanding modern research, the methods originally introduced by Pasteur for the resolution of racemic compounds into their optically active components have undergone comparatively little extension. The following are the methods at present available for this purpose.

(a) *Mechanical Separation of the Crystals.* In a few instances it is possible, by allowing a solution of the racemic mixture to crystallise under certain conditions, to obtain the two enantiomorphs depositing individually—provided they have no tendency to form mixed crystals. If, in addition, the crystals possess characteristic differences of the nature of hemihedral facets or striations, it may be possible to separate them by hand.

This method has a very limited application,[1] since the crystallisation of mechanically separable enantiomorphous forms has been observed in very few cases. It was first utilised by Pasteur in 1848 to resolve racemic acid. On crystallising the sodium ammonium salt of racemic acid at a temperature below 27°, it deposits in the form of the corresponding salts of dextro- and laevo-tartaric acids, *d*- and *l*-$NaNH_4C_4H_4O_6 + 4H_2O$; the crystals have different hemihedral facets and may be separated from one another by hand. If the crystallisation is allowed to take place at a temperature above 27°, the *transition temperature*, there separates out unchanged sodium ammonium racemate $(NaNH_4C_4H_4O_6 + H_2O)_2$.

A modification of this method has been devised by Ostromisslensky,[2] who showed that supersaturated solutions of the *dl*-compounds, on seeding out with a substance which is isomorphous or isodimorphous with the desired enantiomorph, can be made to deposit that form exclusively, the other remaining in solution. The success of this method of separation is entirely independent of the presence of an asymmetric carbon atom in the substance with which the solution is seeded. Optically active asparagine, for example, may be precipitated from a supersaturated solution of *dl*-asparagine by the addition of a crystal of glycine, which is itself inactive.

(b) *Resolution by the Biochemical Method.*—This second method of Pasteur is based on the discovery that when lower organisms, such as bacteria, fungi or yeasts, are allowed to grow in a solution containing a racemic compound, the two enantiomorphs are destroyed at different rates (selectively assimilated), so that an excess of one of the active forms accumulates in the solution.[3] Thus Pasteur found that when *penicillium glaucum* was cultivated in a solution of ammonium racemate, the *d*-tartrate was preferentially destroyed, leaving a solution of ammonium *l*-tartrate. In actual practice this method is only of use in comparatively few cases.

[1] For the resolution of lactic acid by this means, see Purdie, *J. C. S.*, 1893, 63, 1143.
[2] Ostromisslensky, *Ber.*, 1908, 41, 3035.
[3] A relationship therefore exists between physiological activity and the configuration of chemical compounds. Emil Fischer has shown the influence of configuration on the ability of the monosaccharides to undergo alcoholic fermentation (*Ber.*, 1894, 27, 2035) and on the enzymatic hydrolysis of glucosides. Optical antipodes frequently differ in their action on the animal organism. *l*-Nicotine, for example, is more poisonous than its enantiomorph (Pictet and Rotschy, *Ber.*, 1904, 37, 1233).

(c) *Resolution by Means of Salt Formation.*—This method depends on the following principle. When a racemic acid A is combined with an optically active, *e.g.* laevorotatory, base B, two salts are formed, namely (*l*-B, *l*-A) and (*l*-B, *d*-A). As may readily be seen by reference to space models, these salts are not enantiomorphous forms, being produced by combination of the same laevo-base with acids of opposite rotation. In general, therefore, they will possess different solubilities and may be separated by fractional crystallisation. From the individual salts it is then possible to obtain the two active acids. For example, if a solution of racemic acid be saturated with the optically active base cinchonicine, the first salt to crystallise out is cinchonicine *l*-tartrate; on the other hand, by employing the base quinicine the salt of the *d*-acid is the first to separate. Similarly by union with an active acid, a racemic base may be resolved into its *d*- and *l*-forms. The method may be extended to the resolution of any racemic compound which will unite with acids or bases. In this manner the great majority of resolutions have been effected.

In certain cases a complication arises owing to the *r* acid combining, for example, with a *d*-base to form the salt (*d* base, *r* acid) in addition to the more usual mixture of (*d* base, *d* acid) and (*d* base, *l* acid). A salt of the first type is termed a **partially racemic compound** (*Ladenburg*).

(d) *Other Resolutions by Means of Active Substances.*—The two components of a racemic acid have been shown by Marckwald and McKenzie[1] to esterify at different rates with the same active alcohol. Employing an excess of the racemic acid, the unesterified acid at the end of the reaction was found to be optically active. When for example *r*-mandelic acid is incompletely esterified with *l*-menthol, the uncombined residual acid is laevorotatory.

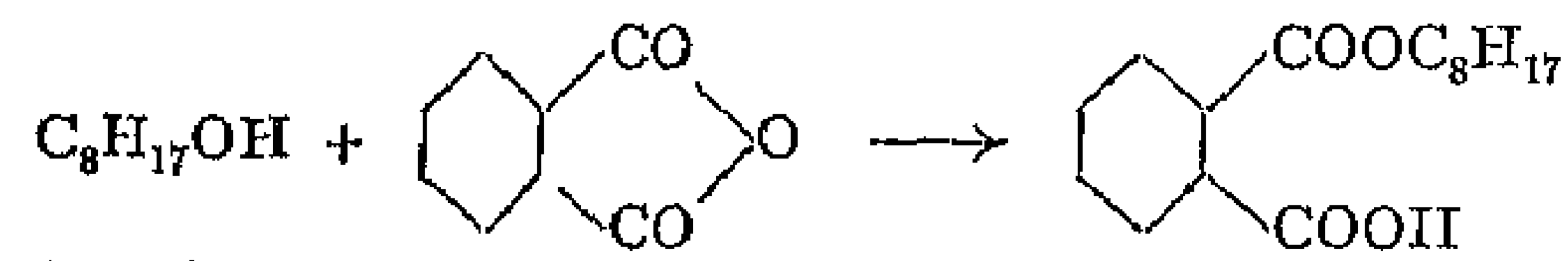
Optically active substances appear in general to react with perceptibly different velocities with the *d*- and *l*-forms of a compound, particularly when the course of the reaction depends in high degree on the constitution of the reagents. A reaction of this type is amide formation, which has also been applied to the resolution of racemic compounds.[2]

Another recent method of resolution is that put forward almost simultaneously by Erlenmeyer, jun.,[3] and Neuberg.[4] According to Erlenmeyer, a racemic base may be resolved by bringing it into reaction with an active aldehyde. In this way active condensation products termed anils are formed, which are separable by fractional crystallisation. The active base may then be regenerated from the anil by hydrolysis with acids.

Racemic alcohols have been resolved by Pickard and Kenyon[5] by

[1] Marckwald and McKenzie, *Ber.*, 1901, **34**, 469. [2] Marckwald and Meth, *Ber.*, 1905, **38**, 801. [3] Erlenmeyer, jun., *Ann.*, 1904, **337**, 307. [4] Neuberg, *Ber.*, 1903, **36**, 1192; **38**, 868. [5] Pickard and Kenyon, *J. C. S.*, 1911, **99**, 45.

combining them with the anhydride of a strong dibasic acid (succinic or phthalic acid) to form acid esters For example,



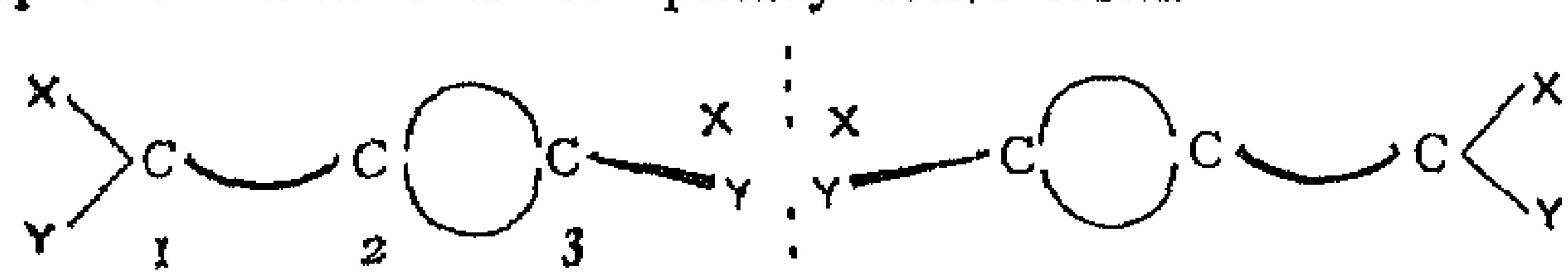
(*dl*-Octyl alcohol) Phthalic anhydride *d*- and *l* Octyl hydrogen phthalates

The racemic acid esters (*e g* octyl hydrogen phthalates) thus obtained are monobasic acids and can be resolved by use of an alkaloid, usually brucine, after which the individual *d*- and *l*-esters can be hydrolysed to give the optically active alcohols

Conditions for Enantiomorphism

A general condition for the occurrence of a compound in optically active forms is that the molecule should exist in two mirror-image structures which cannot be superimposed one upon the other In order that this condition may be fulfilled, it is not essential for the molecule to contain an asymmetric atom in the strict sense of the definition given on p 32 A compound possesses the possibility of existing in enantiomorphous forms provided[1] that the configuration of the molecule is devoid of (1) a plane of symmetry, (2) a centre of symmetry and (3) an alternating axis of symmetry

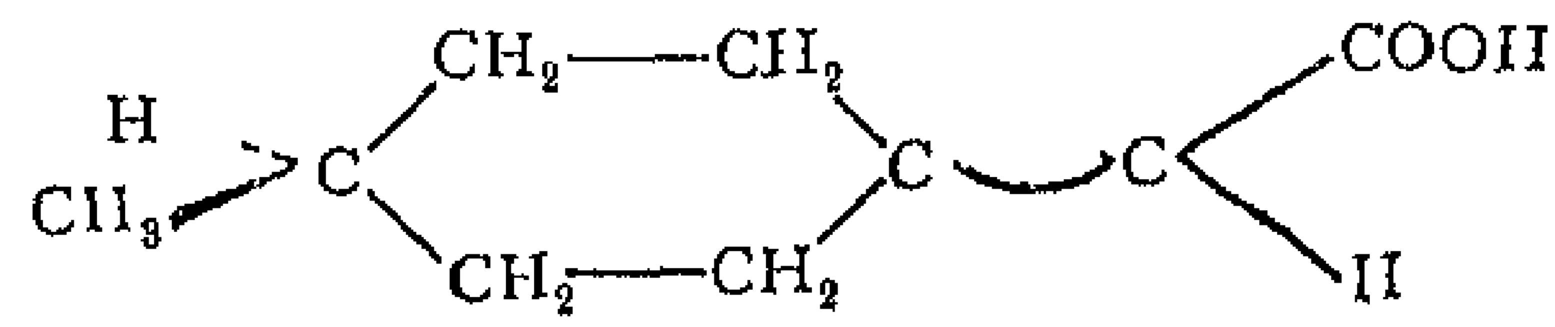
Plane of Symmetry—As has already been stated, the space formula of a compound containing an asymmetric carbon atom is without any plane of symmetry A simple example of a substance containing no asymmetric atom, but for which it is possible to build up two mirror-image and non-superimposable structures, is furnished by allene derivatives of the following type Van't Hoff predicted that these compounds should exist in optically active forms



If we imagine the terminal group XYC (1) to be in the plane of the paper, then owing to the tetrahedral arrangement of the carbon valencies we must represent the double bond between (1) and (2) as lying in a plane at right angles to that of the paper The bond between (2) and (3) will then be in the plane of the paper, leaving X and Y (3) disposed, for example, with X behind and Y in front of the plane As a result of this *spiro*-arrangement (see also *spiro-compounds*, p 51) the structure possesses no plane of symmetry and cannot be superimposed upon its mirror-image So far, however, all attempts to resolve simple compounds of the allene type have failed

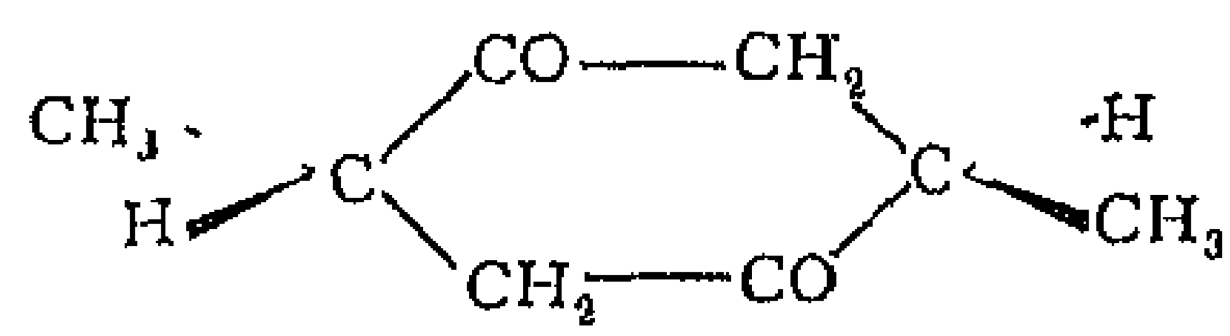
[1] See T V Barker and J E Marsh, *J C S*, 1913, 103, 837

The first successful resolution of a compound containing no asymmetric atom was accomplished by Perkin, Pope and Wallach[1] (1909) in the case of 1-methyl-cyclohexylidene-4-acetic acid By recrystallising



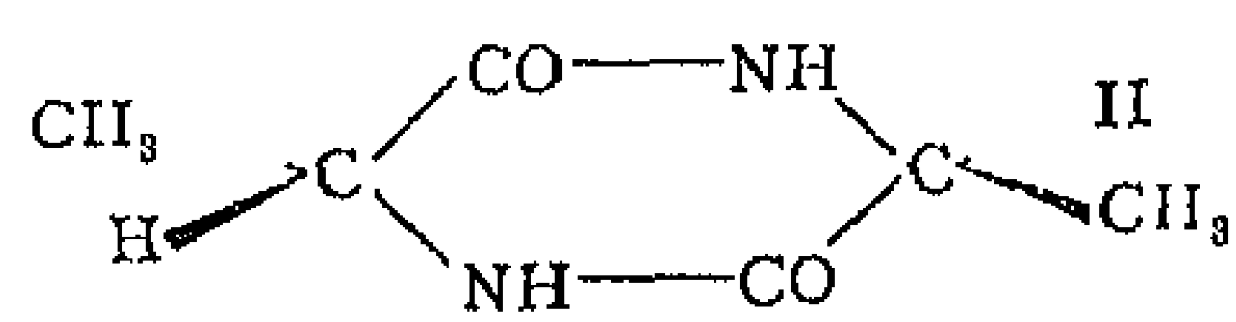
the brucine salts of this acid from aqueous alcohol it was separated into two active components Here also the molecular formula has no plane of symmetry, and two non-superposable mirror-image structures may be built up

Centre of Symmetry—Interesting examples of a new class of inactive and indivisible compounds were discovered among the *trans*-diketo-hexamethylenes (Ladenburg) and the *trans*-diketo-piperazines (Fischer) If in the annexed formula we assume the 6-membered rings



trans-Dimethyl-diketohexamethylene

to lie in the plane of the paper, then the similar *trans*-substituents (*e g* CH_3) must be disposed one behind and one in front of this plane These compounds each possess two similar asymmetric atoms, but are not of the true meso type since there is no plane of symmetry Nevertheless, experiment has shown that compounds of this kind cannot be resolved into active components The real criterion of asymmetry



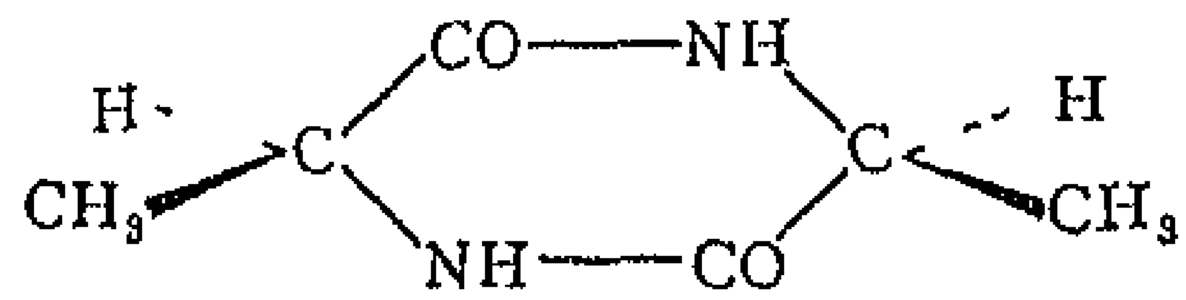
trans Dimethyl diketopiperazine (alanyl anhydride).

is the configuration of the molecule as a whole, and not the relationship existing between two or more atoms within the molecule *On building up the mirror-image of one of the above structures it will be found to be identical with the original, there is therefore no possibility of optical isomerism* A close inspection of the formulæ shows that they all contain a *centre of symmetry*, i e a line drawn from any group to the centre of the molecule (middle of the ring) will, if produced further, meet a similar group

The existence of a centre of symmetry is therefore sufficient to destroy the possibility of optical isomerism Ladenburg described

[1] *J C S*, 1909, 95, 1789

the case of *trans*-dimethyl-diketohexamethylene as one of pseudo-symmetry



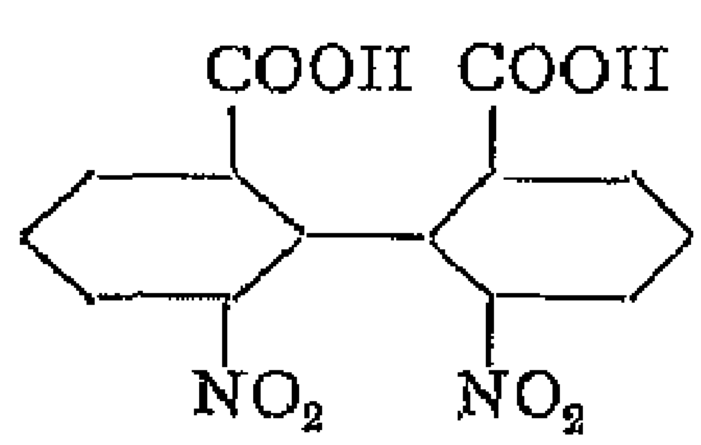
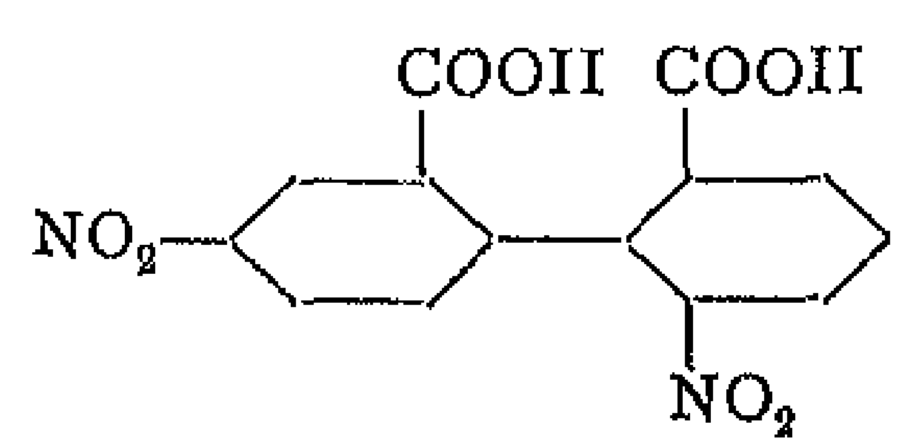
Cis Dimethyl diketopiperazine

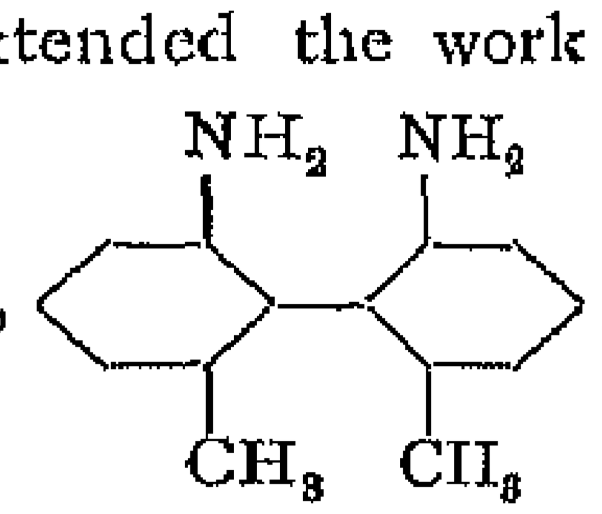
In the *cis*-compounds of the above types there is neither a plane nor a centre of symmetry The *cis*-diketo-piperazines have been found to occur in optically active forms

Alternating Axis of Symmetry — Compounds possessing an **alternating axis** of symmetry are such that on rotating any atom or group round the axis through an angle of 90°, it will, on being reflected across the horizontal plane perpendicular to the axis, come into superposition with a corresponding atom or group Similar atoms or groups alternate successively above and below the plane of reflection and the molecule can be superimposed on its mirror-image This type of symmetry is rarely met with It occurs, for example, among certain substituted cyclobutane derivatives, in which the alternating axis of symmetry is perpendicular to the plane of the ring and the latter corresponds to the plane of reflection (For examples see Barker and Marsh, *loc cit*)

Optical Isomerism in the Diphenyl Series

Optical isomerism of a new kind has recently been found to exist in the diphenyl series (p 486) This development arose from the discovery of Christie and Kenner that it was possible to resolve substituted diphenic acids, such as the 6 6′- and 4 6′- derivatives (I and II) into their optical isomerides

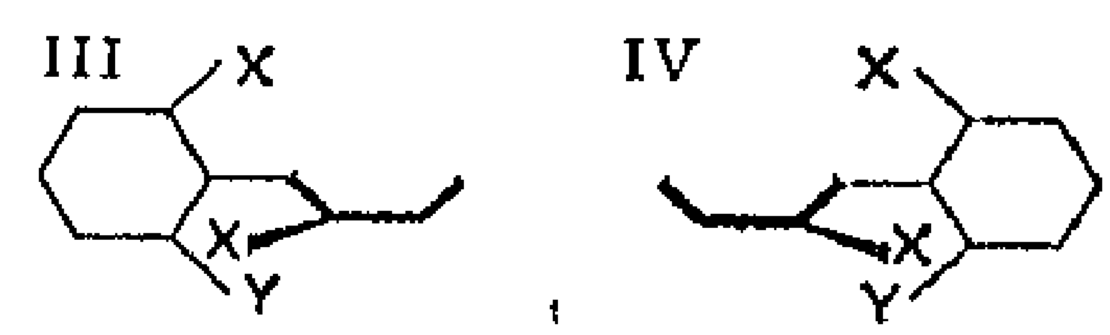
I  II 

Since then a number of substituted diphenic acids have been resolved,[1] and others shown to be incapable of resolution Meisenheimer [2] has extended the work to basic derivatives such as 6 6′-diamino-*o*-ditolyl, , which also exists in enantiomorphous forms

[1] Christie and Kenner, *J C S*, 1922, 121, 614, Christie, Holderness and Kenner, *J C S*, 1926 671 McAllister and Kenner, *J C S*, 1928, 1913, F Bell and J Kenyon, *Chem and Ind*, 1926, 45, 864 [2] *Ber* 1927, 60, B, 1245

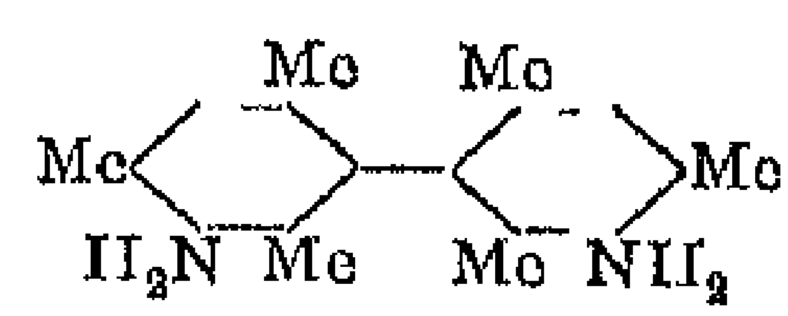
In general, it appears that an essential condition for optical isomerism in the diphenyl series is that at least three of the four positions adjacent to the bond joining the two benzene nuclei should be occupied by substituents

At first some difficulty was experienced in accounting for this isomerism, but a reasonable explanation has been suggested in the theory of restricted rotation, which was advanced independently by[1] Turner and Le Fèvre, Bell and Kenyon, and Mills It is supposed that the free rotation of the benzene nuclei round the bond uniting them is restricted or altogether prevented by the presence of the substituents in the ortho-positions If free rotation is inhibited, it is then possible to build up two non-superimposable mirror-image forms for each of the above compounds (*e g* III and IV)



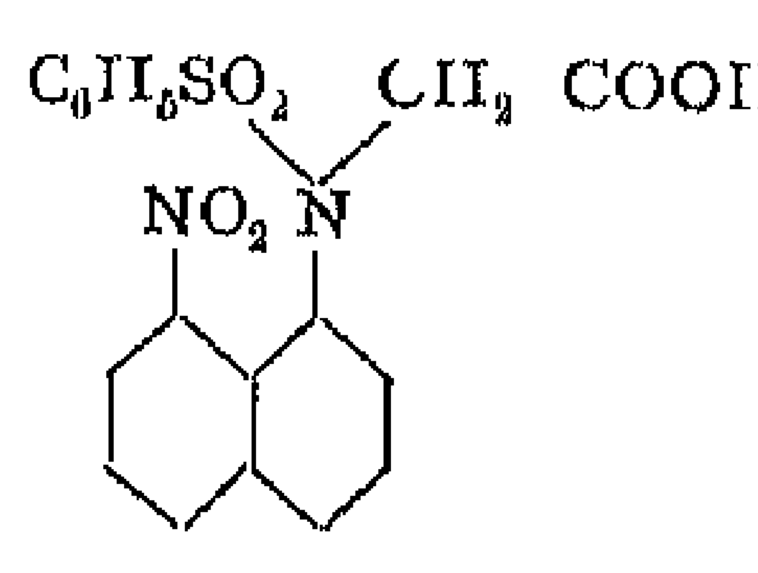
The probability of this explanation becomes evident when actual space models of these derivatives are examined It is then seen that the benzene nuclei are interlocked The actual nature of the force preventing rotation is still an open question, it may be a purely mechanical obstruction or electropolar forces may be involved. But the success of Moyer and Adams[2] in resolving 3 3'-diamino-dimesityl, in which the four ortho groups are identical and practically non-polar, strongly supports the theory of mechanical blocking

All attempts to resolve compounds such as 4 4'-dinitro-diphenic acid and 3 3'-dichloro-diphenyl-5 5' dicarboxylic acid have resulted in failure



The case of 6 6' dinitro-diphenic acid illustrates the fact that complete asymmetry is not an essential condition for optical isomerism, since the compound occurs in two non-superposable forms As in many other cases, the molecular structure of this compound possesses certain elements of symmetry and is therefore described as ***dissymmetric*** rather than asymmetric

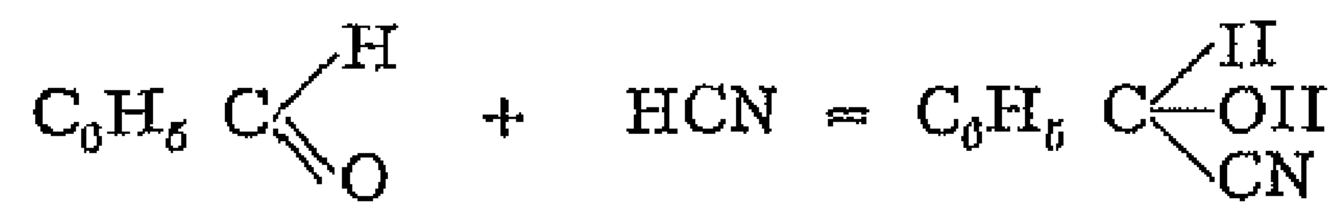
Optical isomerism due to restricted rotation round a single bond would be expected to occur in other compounds besides the diphenyl group Further support for the theory has been furnished by the success of Mills and Elliot[3] in resolving the benzene sulphonyl derivative of 8-nitro-1-naphthyl glycine In this case the optical isomerides are less stable, and the rotatory power disappears in the course of a few hours



[1] Turner and Le Fèvre, *Chem and Ind*, 1926, 45, 831, Mills, *ibid*, 883, 905 Bell and Kenyon, *ibid*, 864 [2] W W Moyer and R Adams, *J Amer Chem Soc*, 1929, 51, 630 [3] Mills and Elliot, *J C S*, 1928, 1291 See also Meisenheimer, *Ber*, 1927, 60, B, 1245

Asymmetric Synthesis

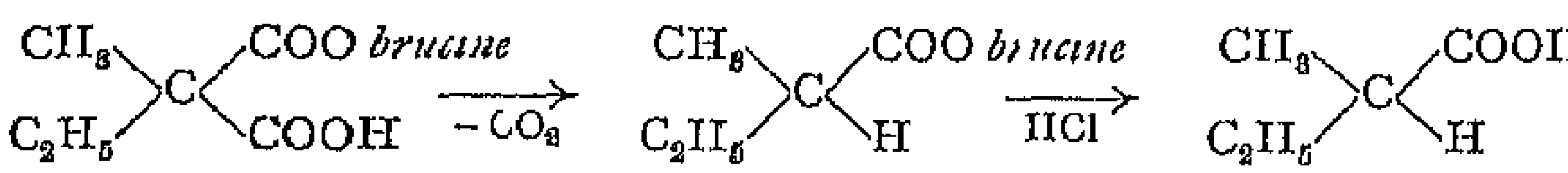
It has already been stated that when a symmetrical compound is converted by ordinary chemical reaction into one of asymmetric type, the new product is not optically active but is of the racemic variety, *e.g.*



Benzaldehyde *dl*-Mandelonitrile

The ordinary chemical and physical properties of the optical isomerides (*e.g.*, the *d*- and *l*-mandelonitriles in the above equation) are identical and there is no reason why the one form should be produced in greater amount than the other. If, however, such a reaction is carried out under the influence of an optically active grouping which is subsequently removed, the product may be found to exhibit optical activity. A synthesis of this kind is termed an *asymmetric synthesis*.

Marckwald[1] in 1904 claims to have effected the first asymmetric synthesis by preparing an active *l*-valeric acid from the acid brucine salt of methyl ethyl malonic acid, by heating the latter at 170°.



In the same year A. McKenzie prepared a laevorotatory atrolactic acid by treating *l*-menthyl benzoylformate with one molecular proportion of methyl magnesium iodide,[2] and subsequently removing the menthyl grouping by hydrolysis.

$$C_6H_5\cdot CO\cdot COOR \longrightarrow C_6H_5\cdot \overset{\displaystyle OH}{\underset{\displaystyle CH_3}{C}}\cdot COOR \longrightarrow C_6H_5\cdot \overset{\displaystyle OH}{\underset{\displaystyle CH_3}{C}}\cdot COOH$$

Benzoyl formic ester Atrolactic acid

McKenzie[3] has recently observed that optically active ketonic esters of the type $C_6H_5\cdot CO\cdot COOR$ and $CH_3\cdot CO\cdot COOR$ undergo mutarotation in alcoholic solution, and that the direction of this change appears to be intimately related to the sign of activity (*d*- or *l*-) of the hydroxy acids produced in the above reactions. On this basis an alternative explanation of the asymmetric synthesis is advanced. It is assumed that a similar mutarotation proceeds instantaneously in the ether employed in the Grignard reaction, leading in the case of *l*-menthyl benzoyl formate to the production of an unequal mixture of

$$\overset{d}{C_6H_5\cdot CO}\cdot\overset{l\text{-}}{COOC_{10}H_{19}} \quad\text{and}\quad \overset{l\text{-}}{C_6H_5\cdot CO}\cdot\overset{l\text{-}}{COOC_{10}H_{19}}$$

and containing a preponderance of the latter. The excess of highly laevorotatory isomeride is supposed to govern the course of the subsequent reaction, and by *asymmetric induction* to result in the formation of a laevorotatory hydroxy acid.

[1] *Ber.*, 1904, **37**, 349, 1368. The actual mechanism by which active valeric acid is formed in these reactions has been the subject of discussion. [2] McKenzie and co-workers, *J. C. S.*, 1904, **85**, 1249. See also 1906, **89**, 365, 688. [3] A. McKenzie and Miss A. G. Mitchell, *Biochem. Zeit.*, 1929, **208**, 456, 472; 1930, **224**, 242.

The following asymmetric syntheses are also due to McKenzie and his co workers

When an ester of pyruvic acid is reduced, it is converted into a lactic ester, with the simultaneous creation of an asymmetric atom By reducing *l*-menthyl or *l*-bornyl pyruvates in an aqueous solvent with aluminium amalgam, McKenzie obtained lactic esters which on hydrolysis gave a lactic acid containing an excess of *l*-acid Similarly the *d*-amyl ester led to the formation of an excess of *d*-lactic acid,[1]

$$\underset{\text{Pyruvic ester}}{CH_3\ CO\ COOR} \longrightarrow \underset{\text{Lactic ester}}{CH_3\ CHOH\ COOR} \longrightarrow \underset{\text{Lactic acid}}{CH_3\ CHOH\ COOH}$$

A further asymmetric synthesis effected by McKenzie and Wren is based on the oxidation of fumaric acid to racemic acid by means of potassium permanganate[2] The oxidation of *l*-bornyl fumarate produced

$$\begin{array}{l} CH\ COOR \\ \| \\ CH\ COOR \end{array} \longrightarrow \begin{array}{l} CHOH\ COOR \\ | \\ CHOH\ COOR \end{array}$$

a mixture of *d*- and *l*-tartaric esters containing an excess of bornyl *l*-tartrate, and on removing the bornyl group a laevorotatory tartaric acid was obtained By using *d*-bornyl fumarate an excess of *d*-tartaric acid was formed

Rosenthaler[3] showed that the combination of aldehydes with hydrogen cyanide in the presence of enzymes gives rise to active cyanhydrins Benzaldehyde and HCN in the presence of emulsin yield optically active *d*-mandelonitrile, which on hydrolysis gives an active *l*-mandelic acid Similar results were obtained by Bredig and Fiske,[4] who used optically active alkaloids in place of enzymes Quinine for example, gives a laevorotatory mandelonitrile and quinidine a dextrorotatory product

Many attempts have been made to produce optically active substances by generating asymmetric compounds under the influence of circularly polarised light or an asymmetric arrangement of polarised light and magnetic field The former method was suggested independently by Le Bel and van't Hoff but has not yet been realised experimentally

Asymmetric Decomposition

A somewhat different procedure has been advocated by Cotton, who discovered that copper *d*- and *l*-tartrates in alkaline solution exhibit circular dichroism, a *d* circularly polarised ray, for example, being more strongly absorbed by the *d*-salt than by the *l* compound (*Cotton effect*) Hence Cotton tried to decompose a solution of the racemate with *d* circularly polarised light in the hope of obtaining a mixture containing an excess of *l*-tartrate No activity could be observed, however After

[1] *J. C S.*, 1905, **87**, 1373, 1909, **95**, 544, 1105 [2] *J C S*, 1907, **91**, 1215 It may be noted that maleic acid on oxidation yields mesotartaric acid [3] *Biochem Zeit*, 1909, **14**, 238, **17**, 257, **19**, 186 [4] *Biochem Zeit*, 1912, **46**, 7

many fruitless attempts along these lines on the part of various investigators, success has finally been achieved by Werner Kuhn,[1] and S Mitchell[2] Kuhn made use of *dl*-α-azidopropionic dimethylamide, CH_3 CHN_3 CO $N(CH_3)_2$ This was found to have an absorption band due to the azido-group, situated in the ultra-violet region at $\lambda = 2900$ Å U., in the neighbourhood of which the rotation rose enormously On passing *d*-circularly polarised light of the same order of wavelength (chiefly $\lambda = 3135$) through the solution, decomposition ensued with the liberation of nitrogen, the recovered dimethylamide having the rotation, $\alpha_{5780} = +0\ 78°$ ($l = 1$) When *l*-circularly polarised light was employed the product had $\alpha_{5780} = -1\ 04°$

The asymmetric photochemical decomposition of humulene nitrosite effected by Mitchell has the merit of simplicity, since it was brought about by the use of visible light in the red part of the spectrum (6000–7800 Å U), and the change could be followed throughout by polarimetric readings Humulene is an inactive sesquiterpene which combines with nitrous anhydride to form a racemic nitrosite A solution of the latter in ethyl butyrate on being irradiated with *l*-circularly polarised light of the above wavelength showed a gradually increasing *d* rotation (maximum value $\alpha_{5780} = +0\ 30°$) which eventually fell during the course of sixty four hours to zero, by which time the decomposition of the nitrosite was complete Similar rotations of the opposite sign were obtained in a parallel experiment with *d* circularly polarised light

These syntheses of active compounds from racemic material are not asymmetric syntheses in the usual sense of the word but are akin to Pasteur's resolutions with bacteria or moulds, which feed preferentially on one of the active forms in a solution of the racemate

The causes which first led to the formation of optically active compounds in nature have been the subject of much speculation The successful photochemical decompositions outlined above indicate one possible solution of the problem, since ordinary daylight is well known to contain under certain conditions a small proportion of circularly polarised light[3] But whatever the original source of the activity, it is probable that the great majority of highly active substances now elaborated by animal and vegetable organisms are formed by asymmetric syntheses under the influence of optically active enzymes or other products (alkaloids, carbohydrates, etc) already present in the organism

B Geometrical Isomerism

The tetrahedra representing two carbon atoms united by a single bond are in contact at one point only, and capable of independent rotation about their common axis If this were not so, even the

[1] W Kuhn and E Knopf, *Zeit phys Chem*, 1930, B, 7 (4), 292 [2] S Mitchell, *J C S*, 1930, 1829 [3] Byk maintains that ordinary diffused daylight contains a small preponderance of one form of circularly polarised light (*Zeit phys Chem*, 1904, 49, 662)

simplest compound of this type, such as ethane, $H_3C—CH_3$, should exist in innumerable modifications. There is, however, only one ethane known. Stereoisomerism is therefore not possible with ethane derivatives unless the carbon atom is asymmetric. As suggested by Wislicenus, it is probable that the atoms or groups united to the two carbon atoms exert a mutual directive influence on each other, until by rotation about the common axis the whole system is transformed into the most stable configuration.

The case is otherwise with doubly bound carbon atoms as contained in ethylene derivatives of the general formula $abC{:}Ccd$. All independent turning of the tetrahedra ceases here, since two corners of each are in union, with a whole edge in contact, and the remaining four valency bonds lying fixed in one plane.

For this reason compounds of the formula $abC{:}Cab$ (and also of the general structure $abC{:}Ccd$) exist in two stereoisomeric forms, corresponding to the configurations

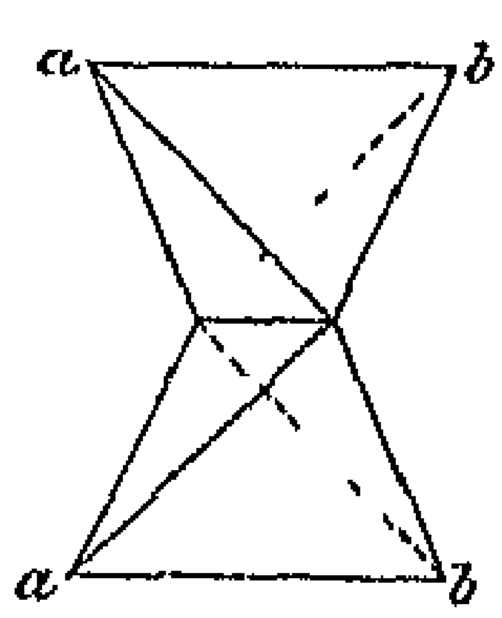


FIG. 10

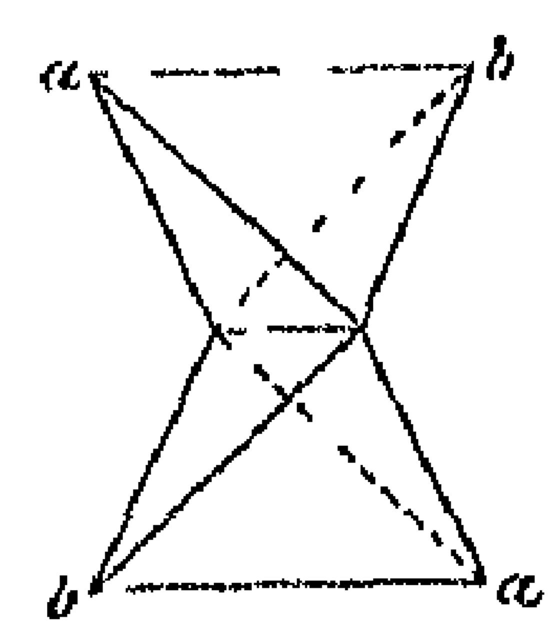


FIG. 11

By projection on to a plane parallel to that containing the four radicals, these formulæ may be simplified to

$$\text{I. } \begin{array}{c} a—C—b \\ \| \\ a—C—b \end{array} \qquad \text{and} \qquad \text{II. } \begin{array}{c} a—C—b \\ \| \\ b—C—a \end{array}$$

Compounds of configuration I, in which similar groups lie on the same side of the molecule, are known as *cis*-forms; they possess one plane of symmetry perpendicular to the axis of the double bond, and another containing C, *a*, *b* and the double bond. Those of configuration II, with similar groups on opposite sides, and having one plane of symmetry containing the axis of the double bond are known as *trans*-forms.

The best known illustration of this type of isomerism is furnished by maleic and fumaric acids.

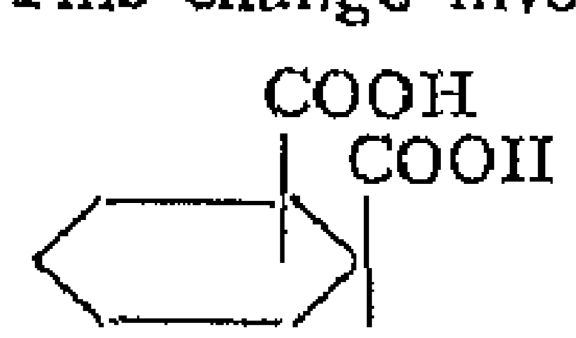
$$\begin{array}{c} H—C—COOH \\ \| \\ H—C—COOH \\ \text{Maleic acid} \end{array} \qquad\qquad \begin{array}{c} H—C—COOH \\ \| \\ HOOC—C—H \\ \text{Fumaric acid} \end{array}$$

In maleic acid the two carboxyl groups lie on the same side of the molecule (*maleinoid* position), and in fumaric acid on opposite sides (*fumaroid* position). The compounds differ not only in physical but also in chemical behaviour (see p. 274). Maleic acid, for example, owing to the proximity of the carboxyl groups, readily forms a stable anhydride, a change not possible in the case of fumaric acid. When strongly heated, fumaric acid is partially transformed into water and the anhydride of maleic acid.

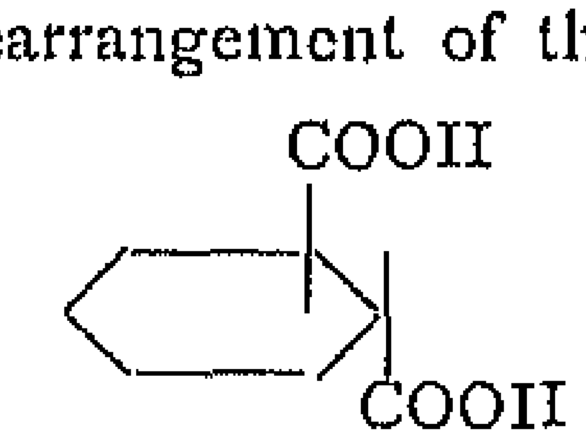
Geometrical isomerism is a common occurrence among those ethylene derivatives in which two different groups are united to each doubly bound carbon atom. Into this class fall the two dimethylethylenes, $CH_3 \cdot CH : CH \cdot CH_3$, crotonic and isocrotonic acids, $H_3C \cdot CH : CH \cdot COOH$, angelic and tiglic acids, $CH_3 \cdot CH : C(CH_3) \cdot COOH$ and many others.

Under certain conditions the geometrical isomers of the ethylene series are interconvertible; thus by heating maleic acid in aqueous solution with a small amount of hydrochloric acid, it is converted into fumaric acid.

A similar geometrical isomerism is found among the cyclic polymethylene compounds, despite their saturated character. In this case, the closed structure of the ring inhibits axial rotation of the carbon atoms in the same manner as the double bond of ethylene derivatives.[1] A comparatively large number of isomerides of this class is known, including the hexahydroterephthalic acids,[2] and the quinitols, $C_6H_{10}(OH)_2$. The existence of isomerism is explained in the same way by assuming that certain groups in the compound may occupy opposing positions in space, in the sense that they may in one case be in proximity, and in the other be removed from one another. A foundation for this explanation is provided by the fact that the one isomer frequently undergoes intramolecular reactions which appear to necessitate neighbouring positions of the groups involved, whereas the other isomer does not undergo these reactions at all. The two hexahydrophthalic acids, for example, exhibit the same relationship as maleic and fumaric acids, as indicated in the following diagrams. The *cis*-acid readily forms an anhydride; whereas the *trans*-anhydride, which is only obtained with difficulty, is converted on fusion into the stable *cis*-anhydride. This change involves a rearrangement of the groups.



Maleinoid or *cis*-acid



Fumaroid or *trans*-acid

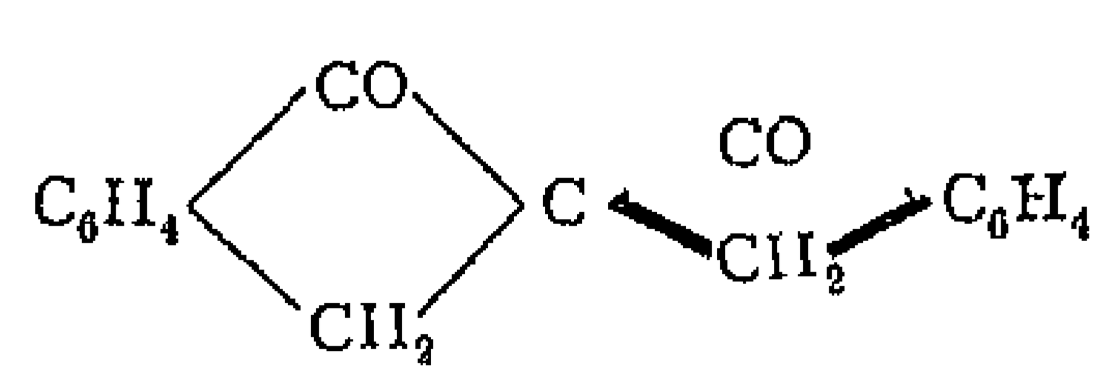
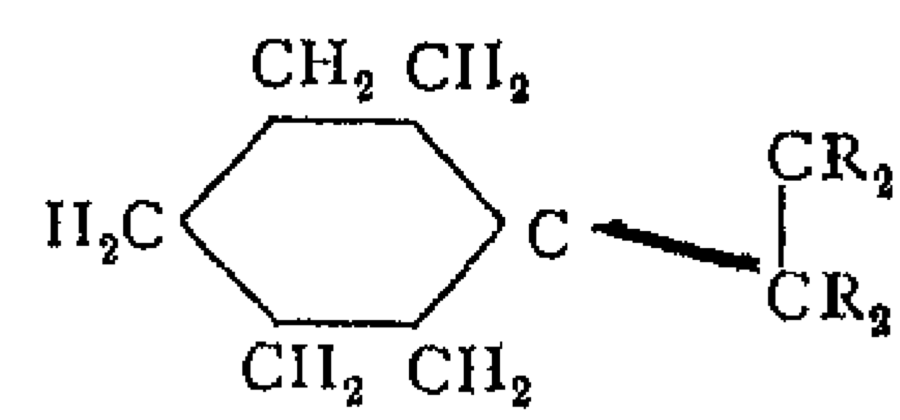
[1] It is also possible to consider ethylene as the simplest example of a molecule with ring structure.

[2] Baeyer, *Ann.*, 1888, 245, 103; 1889, 251, 257; 1890, 256, 1; 258, 1, 145; 1891, 266, 169; 1892, 269, 145.

It may further be mentioned that allene derivatives of the general formula $^{a}_{b}{>}C\ C\ C{<}^{c}_{d}$, or of the simpler type in which c and d are identical with a and b respectively, should exist in two mirror-image forms If in ethylene derivatives the terminal groups attached to the doubly bound carbon atoms lie in one plane, they should be disposed in allene compounds on two planes standing perpendicular to one another Such a configuration possesses no plane of symmetry and the compounds should therefore exist in optically active forms So far all attempts to prepare derivatives of this type suitable for resolution have failed [1]

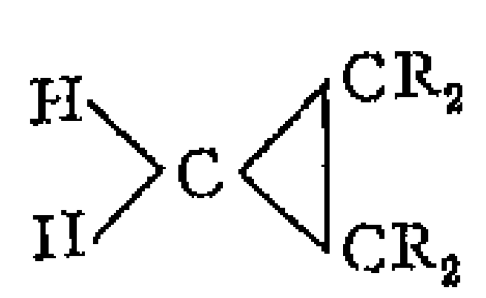
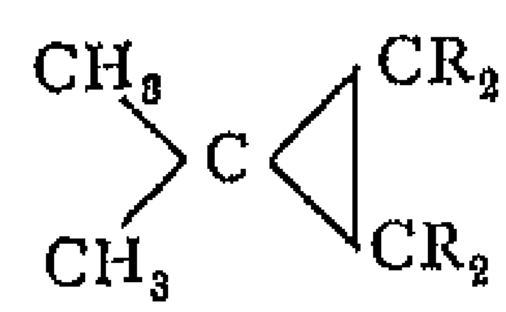
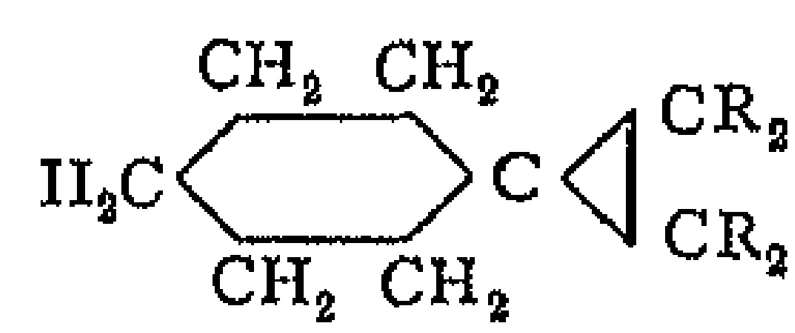
Spiro-compounds

Closely related to the allene derivatives mentioned above are the **spirans** or **spiro compounds** [2] Spirans are cyclic compounds built up of at least two homo- or hetero cyclic rings, and having one ring-atom common to both cyclic structures (I and II) Owing to the tetrahedral arrangement of the bonds around the common atom,[3] the two rings may be regarded as occupying the planes at right angles to each other In many cases the spatial disposition of the groups leads to the occurrence of stereoisomerism

I  II 

Bis 1 hydrindone 2 2 spiran

An extensive investigation has been carried out by Thorpe, Ingold and co workers on the formation and stability of spiro compounds [4] It is well known that in cyclo propane the distortion of the valency bonds from the normal is so great that derivatives of this hydrocarbon are not readily formed and are unstable The above authors have shown that the ease of formation of the cyclopropane ring is increased

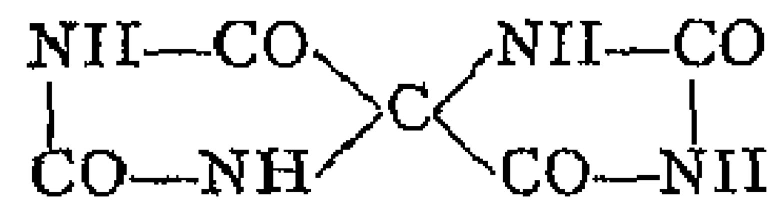
I  II  III 

when the CH_2 group in I is replaced by the *gem* dimethyl group as in II, and to a still greater degree by the cyclohexane group as in the spiro compound III It is therefore concluded that in the simple cyclopropane ring (in which the bonds are calculated to enclose an angle of 60°, as compared with the normal value of 109°28′ for methane) the strain between the carbon bonds is lessened by the introduction of the bulky *gem* dimethyl group, $^{CH_3}_{CH_3}{>}C$, or the cyclohexane residue In the last

[1] *Cf* Dimroth and Feuchter, *Ber*, 1903, 36, 2238 [2] A number of these compounds have been prepared by Fuchs and co workers, *Ber*, 1912, 45, 189, 2114 and later [3] This holds for N as well as C, compare stereochemistry of nitrogen, p 54 [4] *J C S*, 1915, 1080, 1919, 320, 1920, 1579, 1921, 1199, 1922, 1496, 1821, 1923, 122, 3140, 1925, 1678, 1926, 2011

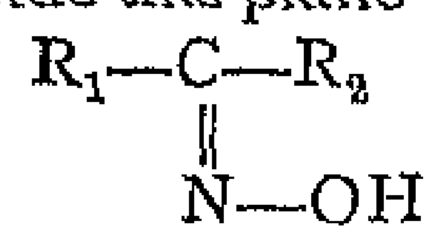
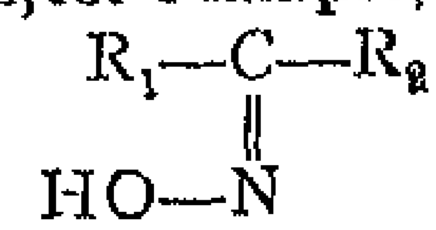
two cases the widening of the angle between two of the bonds by space filling groups may be assumed to bring about a decrease in the angle enclosed by the remaining two bonds, thus facilitating the closure of the ring Once it is formed, the ring in these last-named compounds is under less strain and hence is less liable to disruption

The resolution of *spiro*-5 5-hydantoin by Pope and Whitworth[1] furnishes a remarkably simple example of an optically active spiran



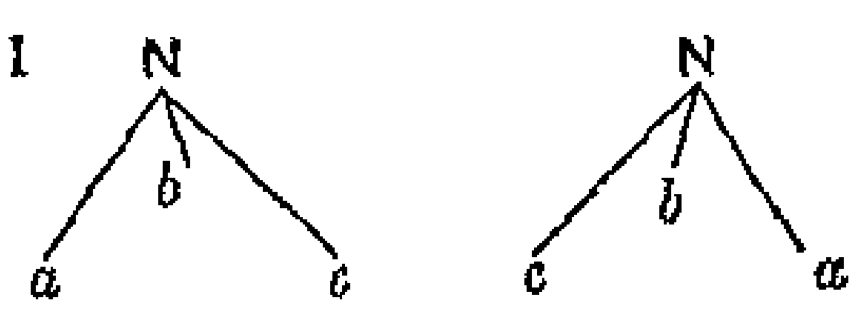
2 Stereo chemistry of Nitrogen[2]

(a) *Optical Isomerism*

The frequent occurrence of oximes and hydrazones, all of which contain the group >C · N—, in geometrically isomeric forms, has been explained by Hantzsch on the assumption that the nitrogen and carbon atoms lie in the same plane as the double bond joining them, with the third nitrogen valency lying outside this plane Oximes, for example, may theoretically be written as  and  and in many cases both forms have been isolated (see p 57 *et seq*)

If the three nitrogen valencies were arranged in this way in tervalent nitrogen compounds of the type N*abc*, the latter would be expected to occur in optical isomerides as in I Many attempts have been made to resolve such compounds but without success For example, no resolution could be effected in the case of benzyl ethyl amine,[3] β-benzylhydroxylamine,[4] methylaniline,[5] tetrahydroquinoline,[5] or hippuric acid[6] by means of active acids

I



It has therefore been concluded that these compounds N*abc* do not occur in enantiomorphous forms Either the three radicals *a b c* lie in the same plane as the nitrogen atom[7] or the system possesses a mobility which brings about rapid racemisation (contrast sulphur compounds, p 61)

(b) *Optically Active Ammonium Salts.*

Corresponding to the asymmetric atom of carbon we have that of pentavalent nitrogen, the five bonds of which are united to different atoms or groups A configuration of this type is represented by the

[1] Sir W J Pope and J B Whitworth, *Chem and Ind*, 1930, 49, 748 [2] For a full treatment see Cohen's *Organic Chemistry*, Vol II, p 294 (Arnold, 1928) [3] Krafft, *Ber*, 1890, 23, 2780 [4] Behrend and König, *Ann*, 1891, 265, 175 [5] Ladenburg, *Ber*, 1893, 26, 864 [6] E Fischer, *Ber*, 1899, 32, 2470 [7] This is apparently contradicted by the fact that ammonia and similar compounds possess a definite dipole moment

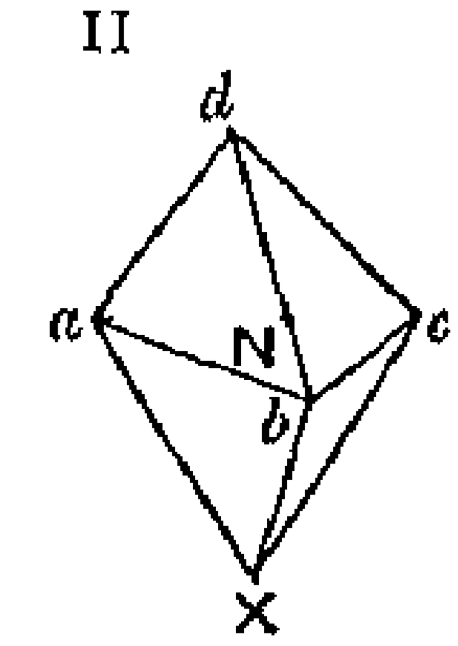
substituted ammonium salts N(*a*, *b*, *c*, *d*)X, which would therefore be expected to exist in two optically active forms of equal and opposite rotation, and an inactive racemic form containing equimolecular amounts of these two isomers

In confirmation of this, Le Bel[1] obtained methyl-ethyl-propyl-isobutyl ammonium chloride, $N(CH_3)(C_2H_5)(C_3H_7)(C_4H_9)Cl$, in a feebly active state by submitting a solution of the salt to the action of the mould *penicillium glaucum* Pope and Peachey[2] prepared the *benzyl-phenyl-allyl-methyl ammonium salt* of *d*-camphorsulphonic acid, and by fractional crystallisation from the non-hydrolysing solvents ethyl acetate and acetone succeeded in resolving it into its enantiomorphous forms The individual *d*-camphorsulphonates, on treatment with potassium iodide, gave the sparingly soluble substituted ammonium iodides of $[\alpha]_D = +52.5°$ and $[\alpha]_D = -51.4°$ respectively These were the first optically pure compounds to be prepared, the activity of which was due to an element other than carbon

These ammonium bromides and iodides are easily racemised, not only in aqueous or alcoholic solution, but also when allowed to stand in chloroform solution (*autoracemisation*) This is supposed to be due to the dissociation of a molecule of alkyl halide followed by recombination in a different manner

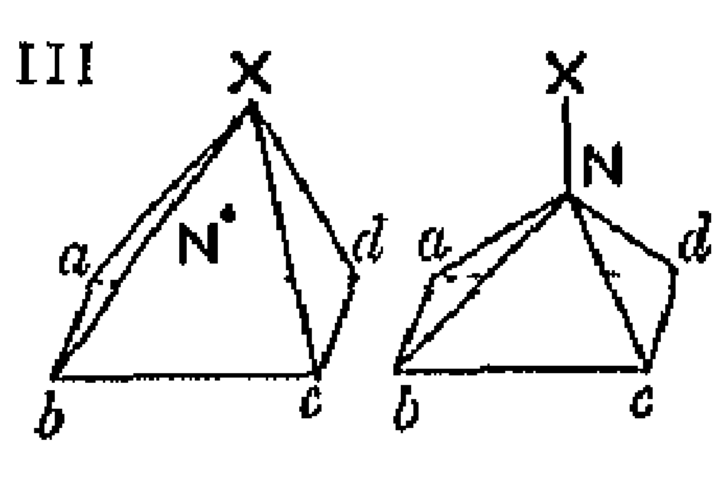
Earlier work on the isomerism of nitrogen compounds led to the consideration of two space arrangements for the pentavalent nitrogen atom In one of these, due to Willgerodt, the five bonds were assumed to lie at the points of a figure obtained by placing two tetrahedra base to base (II) The nitrogen atom was supposed to lie inside the common triangular base *a b c*, with N*a*, N*b* and N*c* representing the valencies of the original trivalent nitrogen Willgerodt's arrangement was subsequently abandoned because it permits a far greater number of isomerides than is actually found in practice, viz, two different optically inactive isomerides Na_3bX, three isomerides Na_2bcX (one of which should be resolvable) and four resolvable forms of N*abca*X

II



The second formula for ammonium compounds, due to Bischoff, represented the N-atom as lying inside a square pyramid X*abcd* (III), with four valencies directed towards the points of the square base and the ionising valency towards the apex This also requires a greater number of isomerides than has been observed For example, compounds of the type N*abcc*X should exist in two forms, one of them resolvable (IV) and the other non-resolvable (V) Similarly, N*abcd*X should occur in three resolvable forms

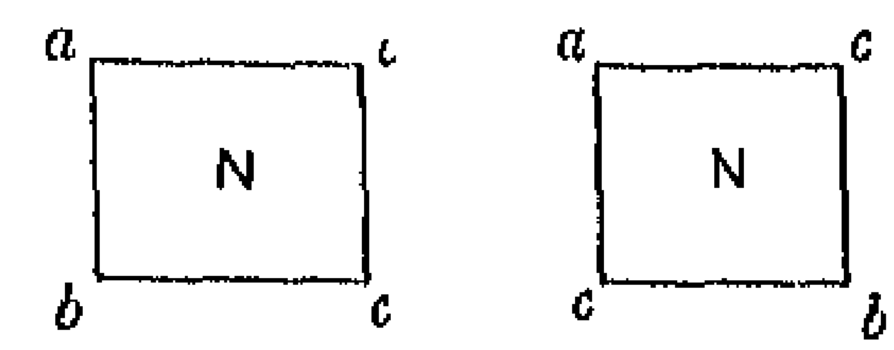
III



[1] Le Bel, *C r*, 1891, 112, 724 [2] Pope and Peachey, *J C S*, 1899, 75, 1127

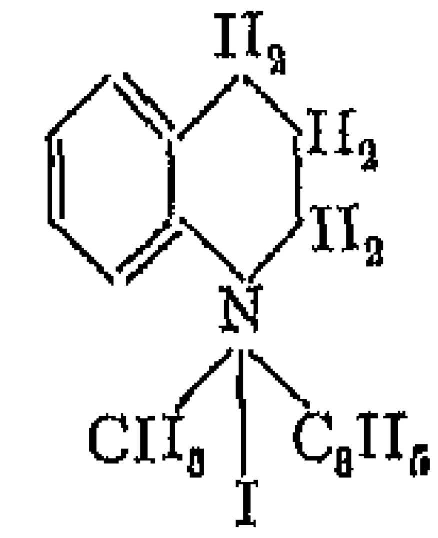
The experimental evidence on which the formulae have to be judged is somewhat conflicting. There are many cases of dimorphism among these salts and in a number of instances supposed isomers have been shown later to be identical. The main facts may be summarised as follows. No optical isomerism has been observed in compounds of the types Na_3bX or Na_2bcX. Compounds of the type $NabcdX$ occur in a single resolvable form, and the same racemic compound is produced whatever the order in which the radicals a, b, c, d are introduced into the molecule.

IV V



As further examples of the large number of compounds $NabcdX$ resolved by Pope, Wedekind, H. O. Jones and others, may be mentioned those built up of phenyl, methyl, benzyl and a series of alkyl radicals,[1] and the cyclic compound, allyl kairolinium iodide (VI).[2]

VI



For some years the Bischoff formula was considered to be in best agreement with the experimental facts. Later it became recognised that the fifth or ionisable valency of nitrogen has no fixed direction with respect to the rest of the atom and is therefore without influence on the asymmetry. This was first expressed by Werner,[3] who formulated ammonium salts with the ionisable group occupying an outer zone and the four radicals in an inner zone. Werner suggested that the stereo-chemistry of nitrogen thus resembled that of methane, the one being present as a positively charged ammonium ion and the other as an electrically neutral molecule.[4]

$$\left[\begin{matrix} R & & R \\ & N & \\ R & & R \end{matrix}\right]X$$

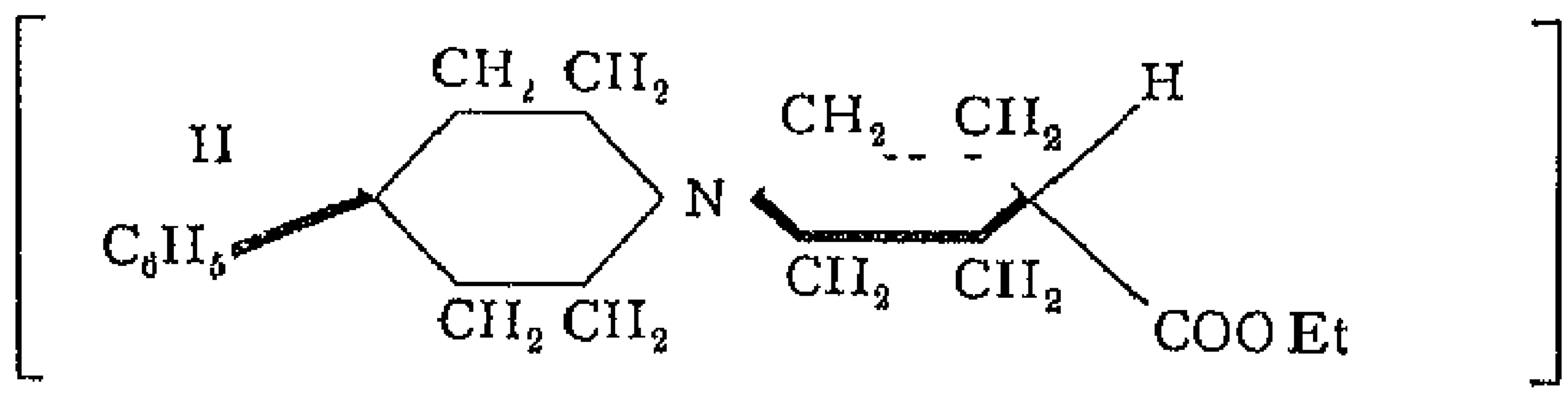
According to modern views the two ions of an ammonium salt are regarded as separate entities, normally held together by the electrostatic attraction of oppositely charged bodies. The individuality of the ions appears to be maintained even in the solid state. Wyckoff,[5] from the X-ray examination of crystals of ammonium chloride, concludes that they are built up of an aggregate of alternating ammonium and chloride ions.

An interesting decision in favour of the tetrahedral as against the pyramidal formula for the ammonium ion has been obtained by the success of Mills and Warren[6] in resolving the following spiro-compound (see p. 51) into its optical isomerides.

The formation of this compound from 4-phenyl piperidine and

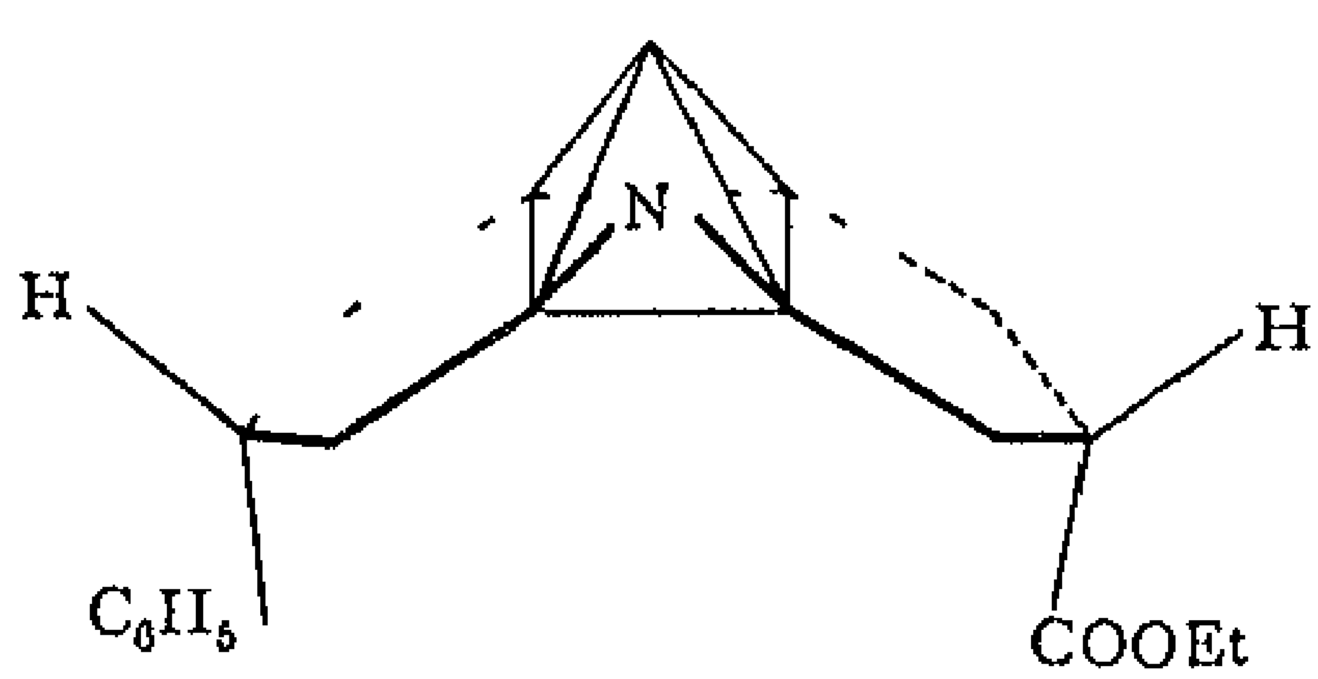
[1] Jones and co-workers, *J. C. S.*, 1906, 89, 208; 1908, 93, 295. [2] Buckney, *J. C. S.*, 1907, 91, 1821. [3] *Zeit. angew. Chem.*, 1906, 19, 1352; New Ideas on Inorganic Chemistry, p. 53. [4] See also H. O. Jones and Dunlop, *J. C. S.*, 1912, 101, 1751. Neogi, *J. Amer. Chem. Soc.*, 1919, 41, 622. [5] *Amer. J. Sci.*, 1922, 3, 177; 4, 173. [6] *J. C. S.*, 1925, 127, 2507.

ac dibromopentane-γ-carboxylic ester took place very readily, and it is therefore assumed that the valency bonds of the nitrogen atom are

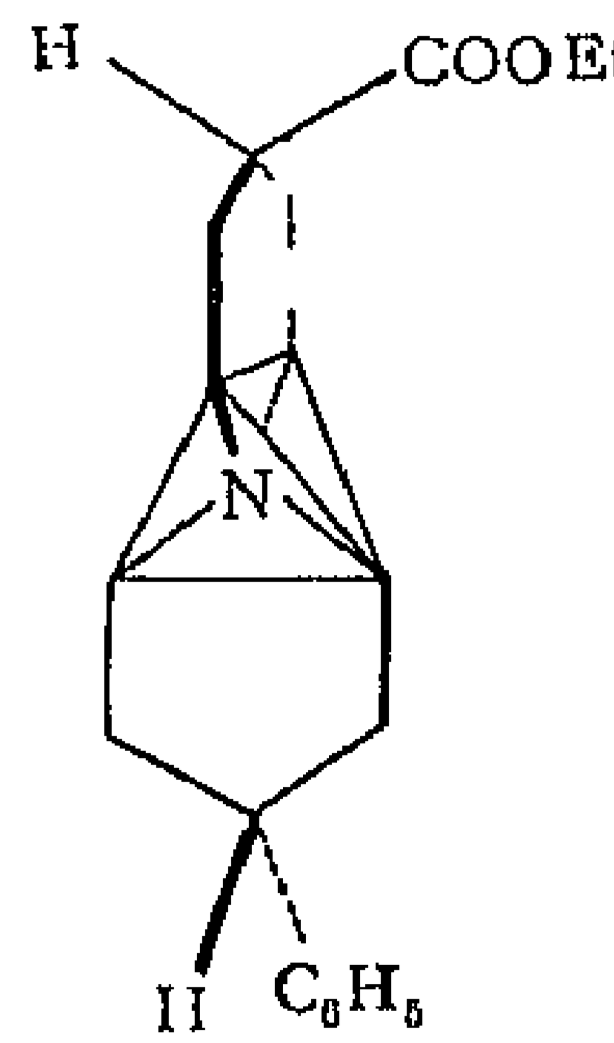


4 Phenyl 4′-carbethoxy *bis* piperidinium-1 1′-spiran-bromide

disposed normally and are not under strain If the arrangement of the N-bonds is tetrahedral, as indicated in the above formula, then the

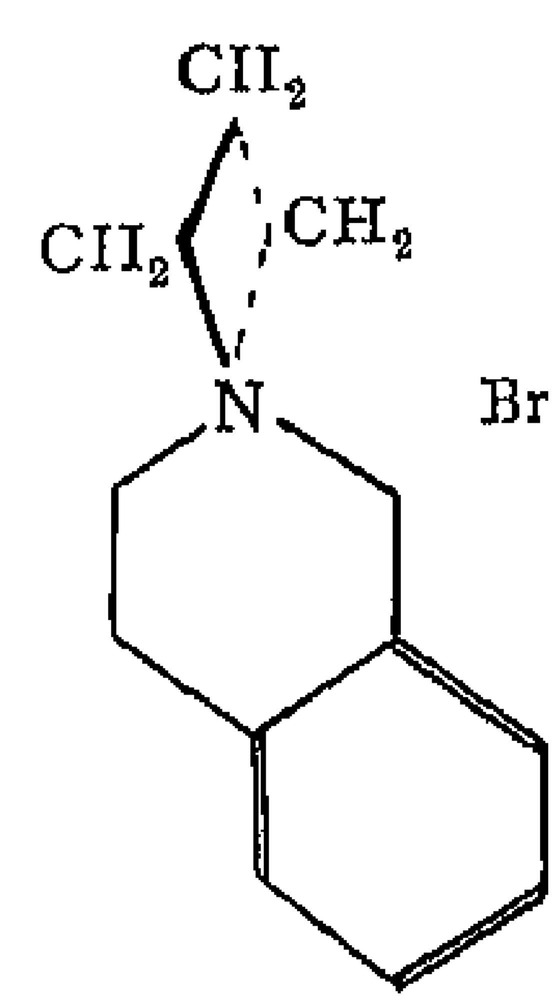


Pyramidal formula



Tetrahedral formula

compound is asymmetric, because the two rings must lie in planes perpendicular to one another, thus bringing the terminal substituents, C_6H_5, H and COOEt, H also into planes at right angles to one another On the Bischoff formula, on the other hand, the compound is symmetrical since in this case the terminal groups lie in one plane which is at right angles to the planes of the two similar rings The resolution was effected by recrystallising the *d*-bromo-camphorsulphonates from acetone



The tetrahedral arrangement of the nitrogen valencies also explains the failure of other workers to resolve compounds such as the trimethylene tetrahydro isoquinolinium salts[1] On the tetrahedral arrangement the plane containing the isoquinoline rings will cut the trimethylene group at right angles, dividing it into two equal halves and thus constituting a plane of symmetry as may be seen from the foregoing figure On the

[1] Jones and Dunlop, *J C S*, 1903, 83, 1400

pyramidal formula of Bischoff the compound is asymmetric in structure and should be resolvable

The Inequality of the Five Valencies of Nitrogen

It has been shown by Meisenheimer[1] that the pentavalent nitrogen compound methyl ethyl aniline oxide $(CH_3)(C_2H_5)(C_6H_5)N=O$, which is prepared by treating the amine with hydrogen peroxide, exists in two optically active forms, despite the apparently identical state of combination of two of the nitrogen bonds Similar isomerism is exhibited by methyl ethyl β naphthylamine oxide and by kairoline oxide, a cyclic amine oxide

We may therefore assume that all amine oxides, $Nabc(=O)$, containing a nitrogen oxygen double bond and three different alkyl radicals attached to the nitrogen are capable of existing in two enantiomorphous forms, although, as indicated by the experiments of Jones, similar compounds of the type $NaabcX$ or $N(=a)bcX$ in which the double bond lies between nitrogen and carbon cannot be resolved into active isomerides This was explained by assuming that in the former compounds the valencies of the double bond, or those united to the two similar radicals, are incapable of binding ionisable groups, whereas in the amine oxides the valency formerly bound to the ionisable acidic group participates with one of the four remaining valencies in the double bond. A fundamental assumption of this theory is the inequality of the five nitrogen valencies in ammonium compounds, it being supposed that the fifth bond, uniting ionisable groups, occupied an abnormal position. The probability of this hypothesis was strengthened by the discovery of Meisenheimer that in compounds of the type $(CH_3)_3NCl_2$, or $(CH_3)_3N(OH)_2$, the chlorine atoms or hydroxyl groups are in different states of combination For example, two different substances of the formula $(CH_3)_3N(OH)(OCH_3)$ are produced according as a salt of trimethylamine oxide is treated with sodium methoxide (I) or the addition compound of trimethylamine oxide with methyl iodide is decomposed by sodium hydroxide (II)

$$\text{I}\quad (CH_3)_3N{=}O \longrightarrow (CH_3)_3N{<}^{OH}_{Cl} \longrightarrow (CH_3)_3N{<}^{OH}_{OCH_3}\ \begin{matrix}(4)\\(5)\end{matrix}$$

$$\text{II}\quad (CH_3)_3N{=}O \longrightarrow (CH_3)_3N{<}^{OCH_3}_{I} \longrightarrow (CH_3)_3N{<}^{OCH_3}_{OH}\ \begin{matrix}(4)\\(5)\end{matrix}$$

The trimethyl hydroxy ammonium methoxide formed in reaction I, quantitatively decomposes into methyl alcohol and trimethylamine oxide on evaporating the aqueous solution The trimethyl methoxy ammonium hydroxide produced in reaction II, on the other hand, yields trimethylamine, formaldehyde and water In addition to the above, several pairs of isomers of the type $(CH_3)_3N(OR')(OR'')$ were isolated All of these could be decomposed to give trimethylamine, aldehyde and alcohol; in each case the alkyl residue occupying position (4) was liberated as aldehyde, and no trace of any other aldehyde could be detected It follows, therefore, that the two alkoxy groups are not linked to nitrogen in the same manner Meisenheimer assumed the five radicals to be attached to nitrogen by means of principal valencies, four in an inner and one in an outer zone (III and IV) as in Werner's theory

$$\text{III}\ \left[\begin{matrix}CH_3\\CH_3\end{matrix}\ N\ \begin{matrix}CH_3\\OCH_3\end{matrix}\right]OH \qquad\qquad \text{IV}\ \left[\begin{matrix}CH_3\\CH_3\end{matrix}\ N\ \begin{matrix}CH_3\\OH\end{matrix}\right]OCH_3$$

It was supposed that the group in the outer zone, at all events when the substance is in solution, resembled the labile group of a tautomeric compound in having no fixed position, and had therefore no apparent influence on the asymmetry of the molecule

An explanation of the constitution of the amine oxides has recently been advanced by Lowry and Sidgwick (see p 30) on the basis of the electronic theory

[1] Meisenheimer, *Ber*, 1908, 41, 3966, *Ann.*, 1911, 885, 117, 1913, 897, 273, 899, 371.

(c) *Geometrical Isomerism of Nitrogen Compounds*

All nitrogen compounds capable of exhibiting geometrical isomerism are characterised structurally by a double bond between carbon and nitrogen, and the isomers bear the same relationship to one another as those of the ethylene series (p 49)

Starting from the consideration that numerous compounds are known in whose molecule a N-atom plays the equivalent part of a CH-group (*cf* benzene and pyridine, naphthalene and quinoline), Hantzsch and Werner suggested that the three valencies of the nitrogen atom are directed towards three summits of a tetrahedron, at whose fourth lies the nitrogen atom itself Hence all compounds containing the divalent group *a*—C—*b* united to the divalent N—*c* should, by analogy with the ethylene derivatives, occur in two different configurations

$$\begin{array}{c} a\text{—C—}b \\ \| \\ d\text{—C—}c \end{array} \quad \text{and} \quad \begin{array}{c} a\text{—C—}b \\ \| \\ c\text{—C—}d \end{array} \qquad\qquad \begin{array}{c} a\text{—C—}b \\ \| \\ \text{N—}c \end{array} \quad \text{and} \quad \begin{array}{c} a\text{—C—}b \\ \| \\ c\text{—N} \end{array}$$

or representing the nitrogen compounds in perspective,

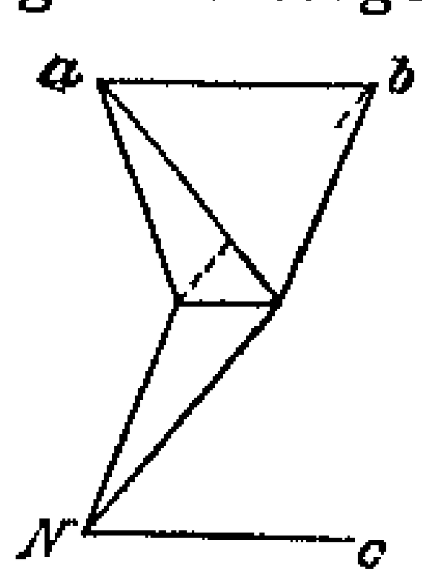


FIG 12

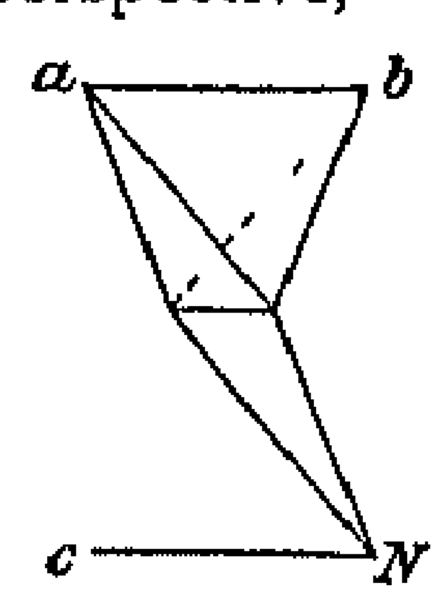


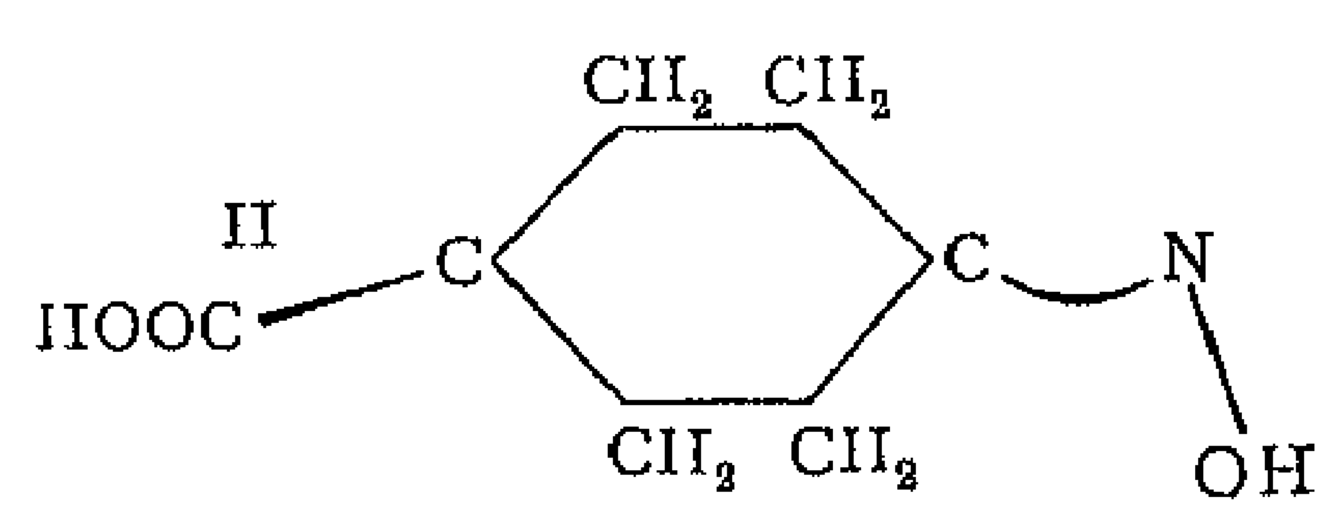
FIG 13

One of the most important and earliest investigated classes of this type is that of the oximes, and in later years inquiry has been extended to the hydrazones, carbazones and imides[1] The two isomeric benzaldoximes, for example, are given the configurations I and II following

$$\text{I}\ \begin{array}{c} C_6H_5\text{—C—H} \\ \| \\ \text{N—OH} \end{array} \qquad \text{II}\ \begin{array}{c} C_6H_5\text{—C—H} \\ \| \\ \text{HO—N} \end{array} \qquad \text{III}\ \begin{array}{c} C_6H_5\text{—C} \\ ||| \\ \text{N} \end{array}$$

Benz-*syn* aldoxime — Benz *anti* aldoxime — Benzonitrile

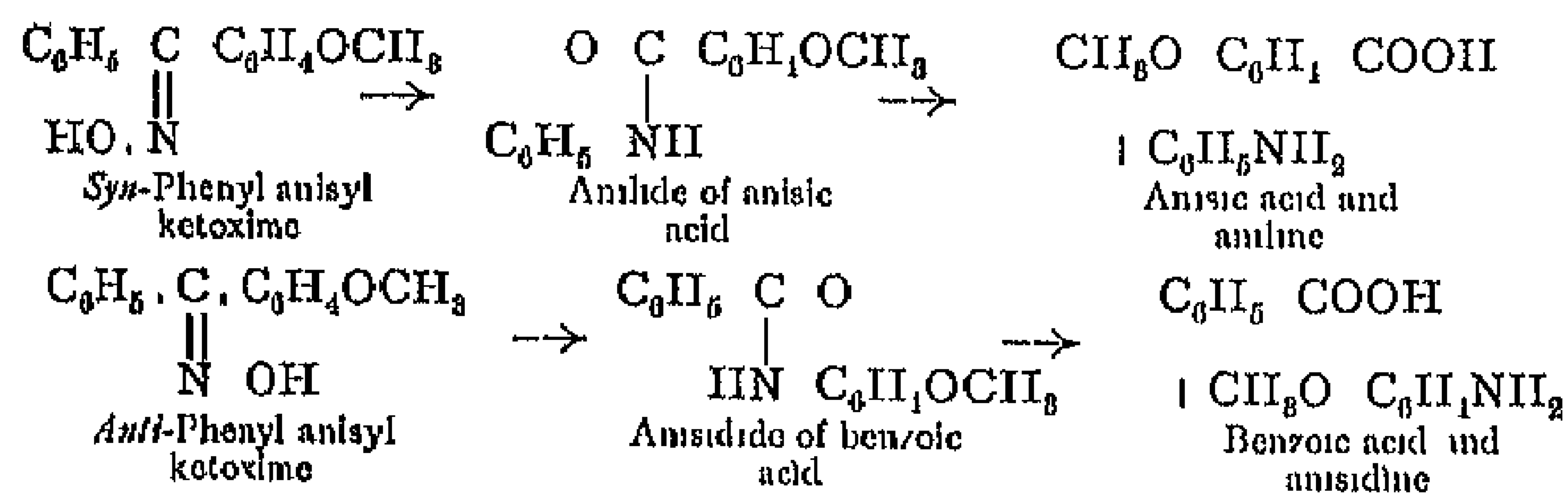
Strong confirmation of this theory is provided by the success of Mills and Bain in resolving the oxime of cyclohexanone carboxylic acid into optically active forms The asymmetry of the compound can only be explained on the assumption that the hydroxyl of the oxime group lies in a different plane to that occupied by the H and COOH at the other end of the molecule



[1] Hantzsch, *Ber*, 1897, 80, 3003 Stieglitz, *Amer Chem J*, 1908, 40, 36 Busch, *Ber*, 1912, 46, 73

The *configurations of stereoisomeric aldoximes* were first deduced by methods devised by Hantzsch. One form readily loses water to yield a nitrile, whereas the other is more stable. It was therefore concluded that in the former, or *syn*-aldoximes, the H and OH are in close spatial proximity, and that in the latter or *anti*-aldoximes the H and OH are on opposite sides of the molecule. More pronounced differences are shown by the acetyl derivatives (p. 431). In some cases only one isomeride is known, the other being presumably too unstable to exist.

As would be expected on the above theory, the symmetrical ketoximes, $R_2C:NOH$, are only known in one form. Unsymmetrical ketoximes, $RR'C:NOH$, exist in many cases in two isomeric forms. Hantzsch deduced the *configurations of the ketoximes* by means of the Beckmann transformation (p. 173), which consists in treating the ketoxime in benzene solution with phosphorus pentachloride, when it is converted into a substituted amide. The two isomers yield different products, and it was formerly assumed that the change occurred in the following manner, the hydroxyl group being supposed to exchange places with the adjacent radical in the *cis*-position, followed by a rearrangement to the substituted amide. As an example we may quote the case of the phenyl anisyl ketoximes.[1]



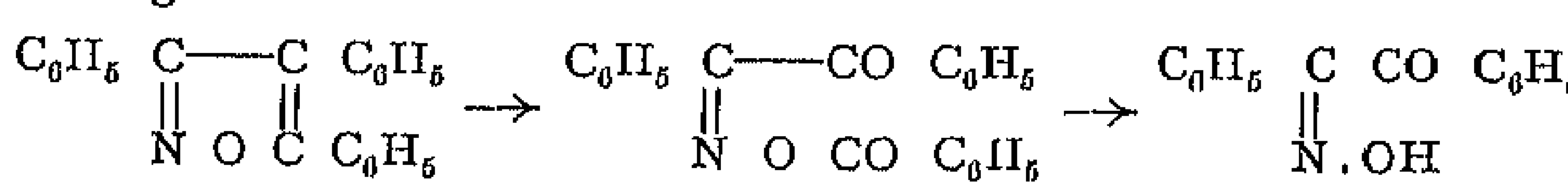
The constitution of the final product is determined by hydrolysis to the acid and amine.

In agreement with theory the symmetrical diketone benzil, $C_6H_5 \cdot CO \cdot CO \cdot C_6H_5$, yields two monoximes and three dioximes (see p. 514).

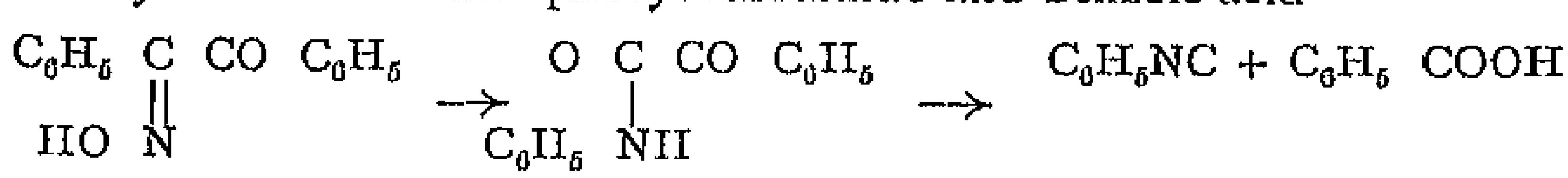
In deriving stereo-chemical formulæ from an examination of intramolecular reactions, it has generally been assumed that such changes proceed all the more readily the closer the reacting groups are to one another in space. Unfortunately, no facts were known by which the validity of this assumption could be strictly tested in the case of the oximes, and there has always remained the possibility that the Beckmann rearrangement, for example, does not involve an interchange of adjacent groups, but of groups in the *anti*-position. The whole

[1] In the aldoximes, the prefix *syn* indicates adjacent positions of the reactive groups H and OH. In the ketoximes the term *syn* or *anti* indicates the position relative to OH which is assumed by the group immediately following the prefix.

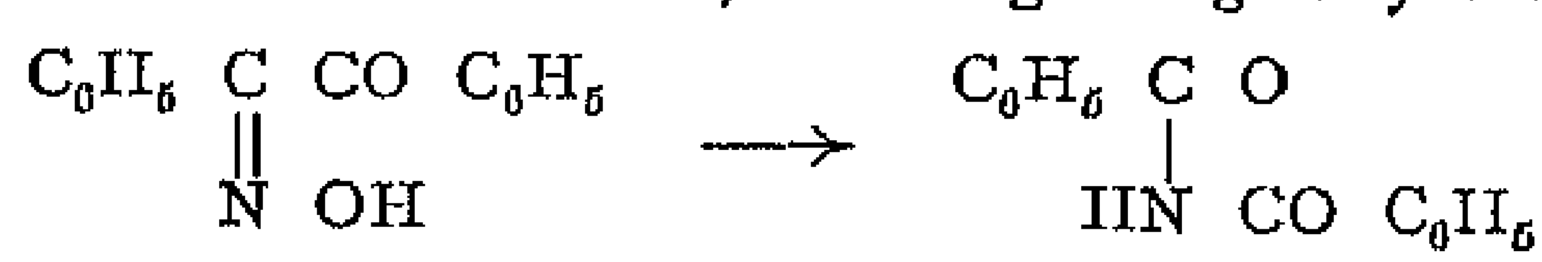
question of the configuration of aldoximes and ketoximes has been reopened in recent years owing to the discovery of reactions which appear to reverse the accepted structures. Meisenheimer[1] found that when triphenyl iso-oxazole (I) is oxidised with ozone or chromic oxide, there is obtained a benzoylated benzil monoxime which on hydrolysis yields a benzil monoxime. We should expect this reaction to proceed according to the scheme

I 

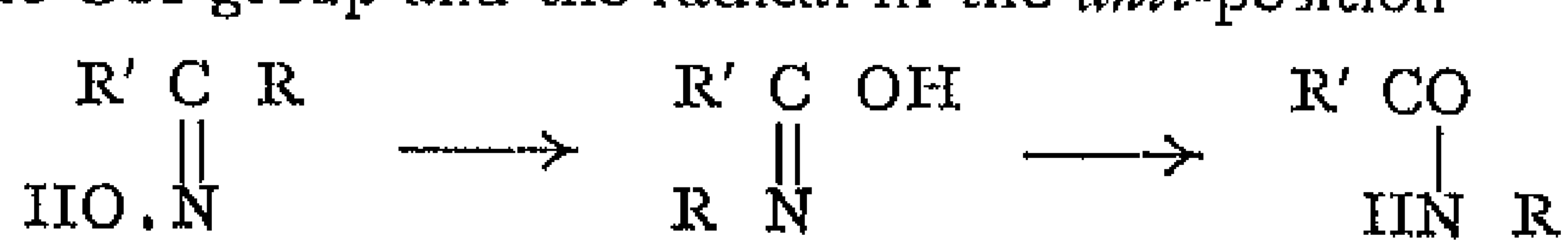
The monoxime actually formed, however, is one which had previously been assigned the alternative structure given below, because when submitted to the Beckmann transformation it may be converted through benzoyl formanilide into phenyl carbamide and benzoic acid.



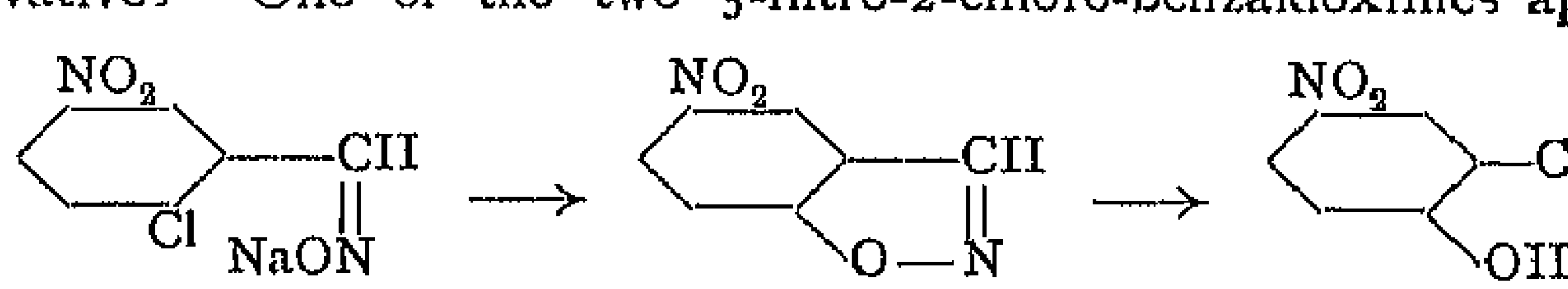
The remaining monoxime of benzil is converted into dibenzamide by the Beckmann transformation, a change originally formulated as



Meisenheimer suggests that the oxidative disruption of triphenyl iso-oxazole may be brought into agreement with the results of the Beckmann change if it is assumed that in the latter an exchange occurs between the OH group and the radical in the *anti*-position.



A similar conclusion appears to be indicated by the work of Bishop and Brady[2] on the conversion of aromatic aldoximes into iso-oxazole derivatives. One of the two 5-nitro-2-chloro-benzaldoximes appears



to undergo this change readily in the form of its sodium salt, the unstable benzo-isooxazole being converted into the nitrile of 5-nitro-salicylic acid, and thus indicating the configuration given above. This isomeride, however, was originally assigned the reverse structure owing to the ease with which the acetyl derivative yields a nitrile.

[1] *Ber.*, 1921, 54, 3206; 1924, 57, 276. *Ann.*, 1925, 444, 94; 1926, 446, 205. [2] O. L. Brady and G. Bishop, *J.C.S.*, 1925, 127, 1357.

Other physical and chemical properties of the stereoisomerides, *e.g.*, acidity, volatility and the formation of co-ordinate complexes provide similarly conflicting evidence,[1] so that for the present the problem remains unsolved. The majority of the workers on this subject, however, have adopted the newer structures proposed by Meisenheimer.

(d) *Geometrical Isomerism in Compounds containing the Group* —N$=$N—

According to Hantzsch the diazo-compounds also exist in stereoisomeric forms, the configurations of which are analogous to those of the ethylene derivatives. The experimental ground for this statement will be dealt with later (see p. 396) but the analogy in question may be illustrated by the following formulæ:

I. Ethylene Compounds

$$\begin{array}{ccc} a\text{—C—H} & \qquad & a\text{—C—H} \\ \Vert & & \Vert \\ b\text{—C—H} & & \text{H—C—}b \\ \textit{Cis form} & & \textit{Trans form} \end{array}$$

II. Carbon-Nitrogen Compounds

$$\begin{array}{ccc} a\text{—C—H} & \qquad & a\text{—C—H} \\ \Vert & & \Vert \\ b\text{—N} & & \text{N—}b \\ \textit{Syn form} & & \textit{Anti form} \end{array}$$

III. Diazo Compounds

$$\begin{array}{ccc} a\text{—N} & \qquad & a\text{—N} \\ \Vert & & \Vert \\ b\text{—N} & & \text{N—}b \\ \textit{Syn form} & & \textit{Anti-form} \end{array}$$

The similarity of configuration can also be shown by use of the tetrahedron models, assuming as before that the valencies of trivalent nitrogen may under certain conditions be directed towards the three corners of a tetrahedron, at whose fourth lies the nitrogen atom itself. From this point of view the diazo-compounds appear as double tetrahedra with one edge in common, as in Figs. 14 and 15.

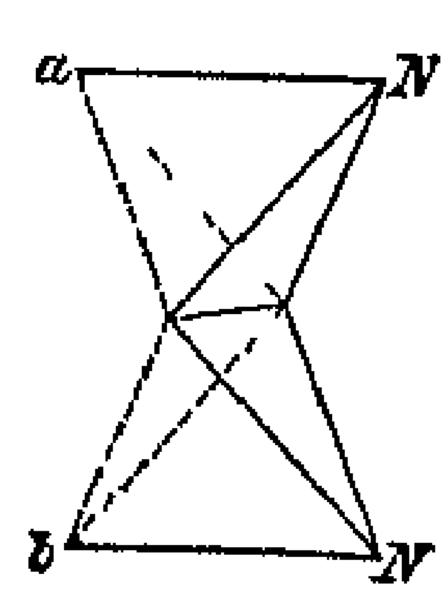


Fig. 14

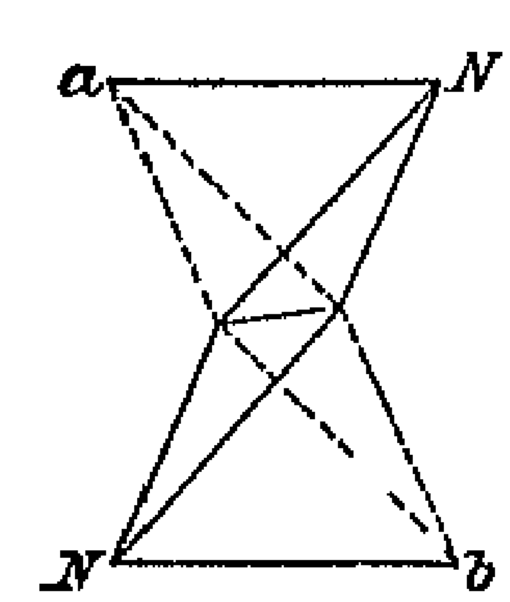


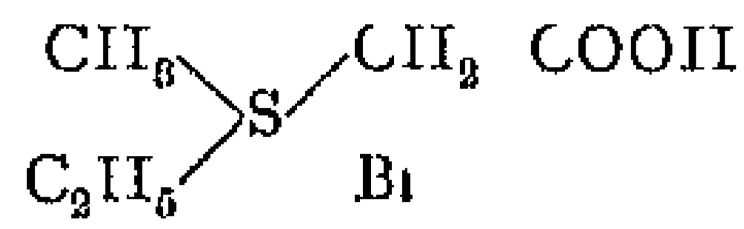
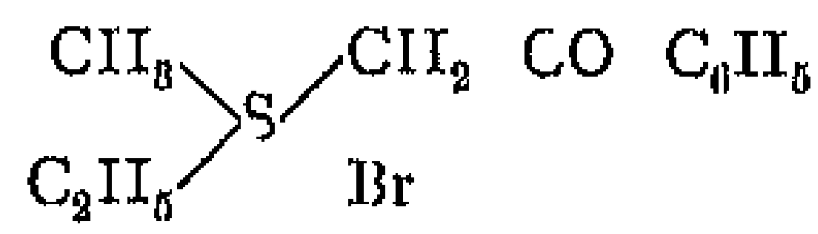
Fig. 15

3. Stereo-chemistry of Sulphur Compounds

The success of Pope and Peachey in resolving a substituted ammonium salt gave a great impetus to the investigation of compounds containing asymmetric atoms other than carbon. *Optically active sulphur com-*

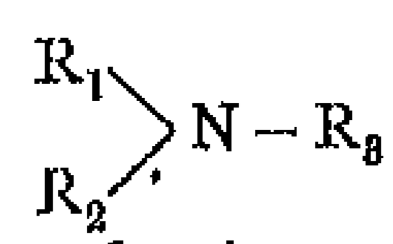
[1] T. W. J. Taylor and E. K. Ewbank, *J. C. S.*, 1926, **129**, 2818; Taylor and M. S. Marks, *ibid.*, 1930, 2302.

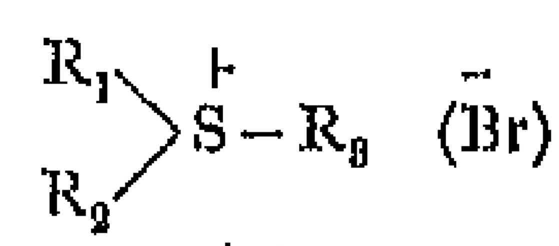
pounds were obtained almost simultaneously by Pope and Peachey[1] and by Smiles.[2] The former resolved methyl ethyl thetine bromide (I) by bringing it into reaction with silver *d*-camphor-sulphonate and repeatedly recrystallising the resulting methyl ethyl thetine *d*-camphor-sulphonates from a mixture of alcohol and ether. The camphor-

I  II 

sulphonic group was then exchanged for platinic chloride, yielding an active double compound containing $PtCl_4$. Smiles resolved the methyl ethyl sulphide addition compound of ω-bromo-acetophenone II in a similar manner using *d*-camphor-sulphonic acid.

The optical activity of these compounds is not destroyed by the ionisation of bromine in aqueous or alcoholic solutions, and is therefore associated with the trisubstituted sulphonium ion. It is noteworthy that no activity has been found in the corresponding trivalent nitrogen


Inactive

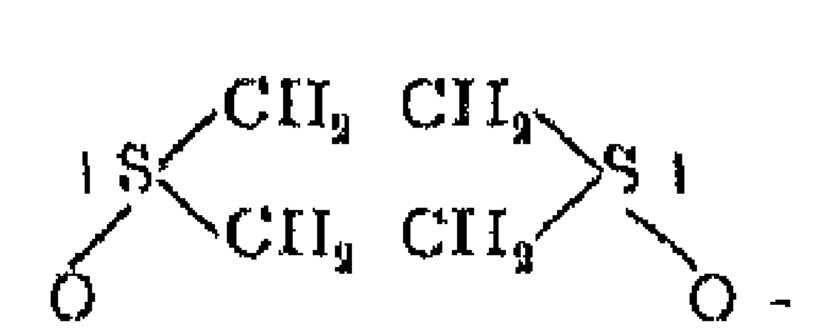

Active

derivatives $NR_1R_2R_3$ despite the apparently identical arrangement of valency electrons around the two central atoms. Lowry has suggested that this is due to the greater mobility of atomic structure in the case of nitrogen.

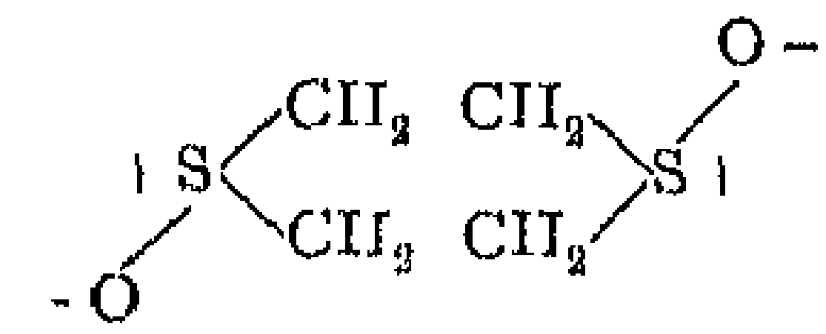
An interesting extension of our knowledge of the stereo-chemistry of sulphur has recently been made. It has been found that sulphinic esters of the type, $CH_3 \cdot C_6H_4 \cdot SO \cdot OC_2H_5$, may exist in the optically active state, a discovery which was followed up by the resolution of *m*-carboxyphenyl methyl sulphoxide $HOOC \cdot C_6H_4 \cdot SO \cdot CH_3$ and 4′-amino-4-methyl-diphenyl sulphoxide[3] $H_2N \cdot C_6H_4 \cdot SO \cdot C_6H_4 \cdot CH_3$. A carbon atom linked to oxygen by a double bond is regarded as having a plane of symmetry bisecting both atoms and the double bond, but no such symmetry can be present in the sulphoxide linking, since sulphoxides exist in mirror-image forms. Sulphur and oxygen are here joined by a semi-polar double bond (see parachor, p. 81) and therefore resemble nitrogen and oxygen in the amine oxides (p. 30). Oxygen is evidently disposed above or below the plane occupied by the group C—S—C, a conjecture which is supported by the isolation of compounds of the type of dithian dioxide in (inactive) *geometrically isomeric forms*,[4]

[1] *J. C. S.*, 1900, 77, 1072. [2] *J. C. S.*, 1900, 77, 1174. See also Pope and Neville. [3] Phillips, *J. C. S.*, 1925, 127, 2552; Harrison, Kenyon and Phillips, *J. C. S.*, 1926, 2079. [4] E. V. Bell and G. M. Bennett, *J. C. S.*, 1927, 1798. For other compounds of similar type see E. V. Bell and G. M. Bennett, *J. C. S.*, 1928, 86; 1929, 15. F. G. Mann and Sir W. J. Pope, *J. C. S.*, 1922, 1052.

the oxygen atoms being arranged in the *cis*- or *trans*-positions with respect to each other



Cis dithian dioxide



Trans dithian dioxide

Asymmetry of Cobalt, Rhodium, Chromium and Iron Compounds See Werner, *Ber*, 1912, **45**, 121, 1913, **46**, 3674

Optically Active Selenium Compounds[1] See Pope and Neville, *Proc. Chem Soc*, 1902, **18**, 198, **21**, 92

Optically Active Tin Compounds See Pope and Peachey, *Proc Chem Soc*, **16**, 42, 116

Optically Active Silicon Compounds Kipping, *J C S*, 1907, **91**, 209

TAUTOMERISM, DESMOTROPISM, DYNAMIC ISOMERISM

There are a number of substances known which appear to exist in one form only, but give rise to two distinct series of derivatives. Familiar examples of this kind are hydrocyanic acid, which may react as hydrogen cyanide H—C≡N or as carbimide C=N—H, and cyanic acid, for which we have the possible formulæ O=C=NH and HO—C≡N

Such compounds, the constitution of which appears to vary with the reagent employed, are called tautomeric The word **tautomerism** therefore, in its original sense, denoted a special case of structural isomerism, in which only one form had been isolated[2]

The earliest explanation of this phenomenon was based on the assumption that the mobile hydrogen atom was in a state of constant oscillation, and in consequence both parent forms could be imagined to be present in the one substance (Laar)[3] The non-existence of one of the expected forms was, however, first explained by postulating the occurrence of a labile modification, having a pronounced tendency to undergo intramolecular rearrangement into the stable isomeride

In the year 1880 Erlenmeyer stated that all secondary alcohols, in which the two affinities of the group =CH OH are united to another carbon atom by a double bond, are at the moment of their formation transformed into aldehydes, and in the same way tertiary alcohols of this type (with the exception of the phenols) isomerise into ketones Those chemical reactions, for example, which might be expected to

[1] For a summary of optically active compounds containing asymmetric atoms other than carbon, see Cohen, *Organic Chemistry*, Part II (Arnold) [2] Our knowledge of dynamic isomerism has been greatly extended in recent years through the work of Thorpe and Ingold These authors adopt *tautomerism* as a general term to cover all examples of chemical change involving the existence of isomers in a state of equilibrium, even though special conditions may be required to bring about this state (see p 64 *et seq*) [3] The word tautomerism was first employed by Laar, in connection with his theory of oscillations

yield vinyl alcohol, $CH_2{=}CH{-}OH$, invariably lead to the formation of the isomeric aldehyde, $CH_3{-}CH{=}O$

Similar conclusions were arrived at by Baeyer in 1883, from his work on the derivatives of isatin He found that the isomerism exhibited by these derivatives (see p 595) disappeared when the parent substance was regenerated in the free state Isatin itself could be isolated in one form only, and the instability of the other theoretically possible isomeride was ascribed to the mobility of an atom of hydrogen, the replacement of which by another group rendered this configuration also stable Baeyer called the labile modification the "pseudo-form"

The oscillation theory of tautomerism was first proposed by Kekulé, in connection with the constitution of benzene (p 357), and later taken up by Laar it assumes the hydrogen atom to alternate rapidly between two extreme positions of equilibrium, the alternation producing a corresponding change of single to double linking, and *vice versa*, between two adjacent carbon atoms

The work of later investigators,[1] however, has shown the explanation advanced by Baeyer to be the correct one Tautomerism is due to the existence of two labile forms in equilibrium with each other, the isomerism in the majority of cases being caused by the transfer of a hydrogen atom from one carbon atom to another which is in close proximity to the first, accompanied by the necessary rearrangement of single and double bonds Nitrogen may also function in the same manner as carbon in this interchange (see p 65)

Knorr has advanced a general theory of tautomerism which is outlined in the following paragraphs Structural isomers which differ only in the position of a hydrogen atom within the molecule are termed *desmotropes*, and in actual practice the isolation of both isomerides of this type has only been attained in a few cases Tribenzoyl methane, for example, has been prepared in the two forms

$$CH\begin{array}{l} \diagup COC_6H_5 \\ -COC_6H_5 \\ \diagdown COC_6H_5 \end{array} \qquad\qquad C\begin{array}{l} /\!\!/ C(OH)C_6H_5 \\ -COC_6H_5 \\ \diagdown COC_6H_5 \end{array}$$

Keto form Enol form[2]

In the vast majority of cases the isomerides are only realisable in the form of derivatives, one parent substance alone being known Such a substance, as already stated, is then called *tautomeric*

Tautomerism therefore depends primarily on one compound reacting in two different forms, and thus giving rise to two series of derivatives This common property of all tautomeric compounds serves as a general definition of the term tautomerism

[1] Wislicenus, *Ann*, 1896, **291**, 147 Hantzsch, *Ber*, 1896, **29**, 699, 2251, 1898, **31**, 2854, 1899, **32**, 575, 1723, 3066, 1906, **39**, 1084 Knorr, *Ann*, 1899, **306**, 332 Lowry, *J C S*, 1899, **75**, 211 Rabe, *Ann*, 1900, **313**, 129 K H Meyer, *Ann*, 1913, **398**, 63 [2] The term "enol" is derived from "en," indicating the double bond, and "ol," representing the alcoholic hydroxyl group

Further sub-classification of these substances is most conveniently based on the degree of mobility of the hydrogen atom.

In cases where both the isomerides predicted by theory have been isolated, these are frequently termed *dynamic isomers* (Lowry) or *desmotropic compounds*, to distinguish them from the single tautomeric substance. Desmotropes are characterised by a tendency to undergo isomerisation into the other form. In general, therefore, they are not stable in solution or in the fluid state. Solution or fusion of either form usually results in the production of a mixture containing the two isomerides in a state of equilibrium. Such a mixture is described by Knorr as an "*allelotropic mixture*". The rates of isomerisation of the two forms may assume all possible values, the same naturally holding true for the ratio of the two isomers in equilibrium, since this itself depends on the relative rates of change.

It frequently happens that the amount of one of the forms in the equilibrium-mixture becomes so small as to be negligible. In such cases this labile form, no longer traceable by analytical methods, corresponds to the pseudoform of Baeyer.

On the other hand, if we imagine the forms in an allelotropic mixture to isomerise with equal and very great velocities, we have a picture of a limiting case conforming to Laar's oscillation hypothesis.

Fluid tautomeric substances, such as hydrocyanic acid (p. 323), would appear to fall under the heading of allelotropic mixtures, except in the limiting cases discussed above.

A solid tautomeric substance can, in most instances, be assigned a definite structure. This, however, cannot be determined with certainty by chemical means, and recourse is usually had to methods involving a comparison of the substance with its derivatives or with other desmotropic isomerides of known constitution. Physical methods are of the greatest value in this connection.

For examples of tautomerism see isatin, p. 595, acetoacetic ester, p. 261, and pyrazole derivatives, p. 614.

A more general view of dynamic isomerism has been adopted in the extensive researches carried out in recent years by Thorpe and Ingold. All examples of dynamic isomerism are classed by these authors under the heading of tautomerism, including cases in which both forms are readily isolated or in which the attainment of equilibrium requires special temperature conditions or the addition of a catalyst. Thorpe and Ingold[1] have revived and extended an earlier classification of Laar[2] by which tautomeric compounds are grouped according to the type of mobile system present, e.g. *dyads*, containing two polyvalent elements linked together, the labile hydrogen atom travelling from one to another of these: *triads* in which the original polyvalent

[1] Quelque nouveaux Aspects de la Tautomerie, *Bull. Soc. Chim.*, 1923. [2] *Ber.*, 1885, 18, 648.

elements are separated by a third, the H-atom now travelling from the first to the third atom in the chain, and so on.

Dyads.—A simple representative of this class is hydrogen cyanide, which is probably a tautomeric mixture of the structures H—C≡N and H—N≚C (see p. 81). Although only one form of the acid is known it yields two series of alkyl derivatives of the types R.CN and R.NC.

Another example is methyl pyrazole (p. 615), which gives rise to two N-phenyl derivatives and may therefore be written as

Methyl pyrazole

Triads.—Triad systems include a large number of types, chief among which are the following:—

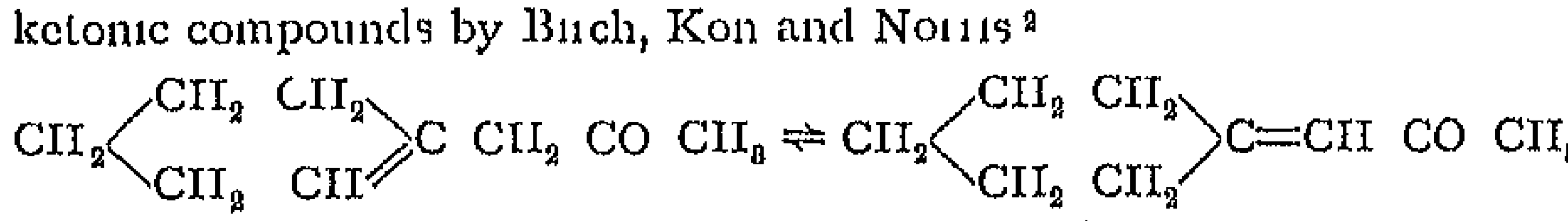
(1) Three carbon system	C—C—C
(2) Diazo amino system	N—N—N
(3) Cyanide imide system	C—C—N
(4) Keto enol system	C—C—O
(5) Amidine system	N—C—N
(6) Amido imidol system	N—C—O
(7) Hydrazone azo system	C—N—N
(8) Nitro pseudonitro system	C—N—O

Only the more important of these can be mentioned here. In the following paragraphs the use of an arrow indicates the alternative position to which the hydrogen atom may travel.

(1) *The Three-carbon System*, C=C—CH. The possibility of tautomerism of this kind is indicated by the transformation of $\beta\gamma$-pentenic acid into the $\alpha\beta$-acid on being boiled with alkali (Fittig[1]). In this case both forms are usually stable and readily isolated. A more

$$CH_3.CH.CH.CH_2.COOH \longrightarrow CH_3.CH_2.CH.CH.COOH$$

mobile isomerism has, however, been shown to occur in the following ketonic compounds by Birch, Kon and Norris[2]



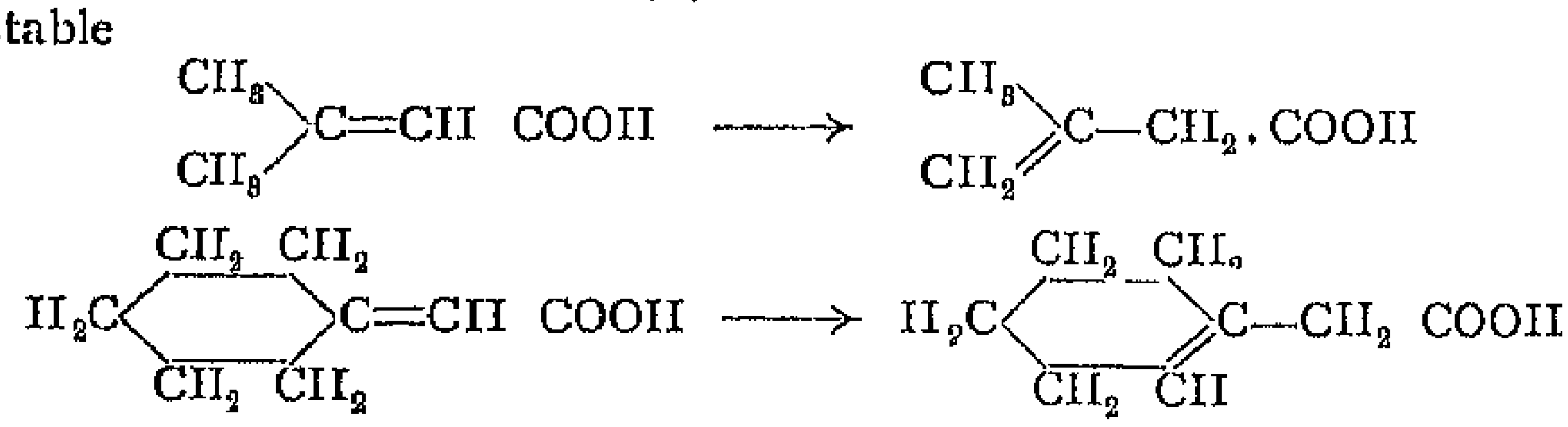
I II

These form an equilibrium mixture containing a very large proportion of I.

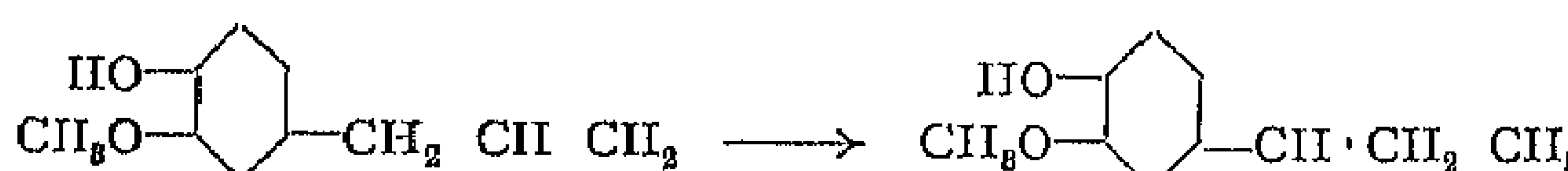
Among the acids investigated by Fittig the direction of the shift was from the $\beta\gamma$- to the $\alpha\beta$-position. Kon and his co-workers, who

[1] *Ber.*, 1891, 24, 82; 1894, 27, 2677; *Ann.*, 1896, 299, 1. [2] *J. C. S.*, 1923, 123, 1361.
T.

have examined a large number of cases of this nature, have shown that the mobility of the hydrogen atom and the relative stability of the two forms depends on the nature of the other groups present in the molecule. For example, in the *gem*-dialkyl acrylic acids and cyclohexylidene acetic acids, the $\beta\gamma$-unsaturated derivatives are the more stable:



A similar isomeric change occurs in the transformation of eugenol into isoeugenol under the influence of hot alkalis, and in many terpene derivatives:

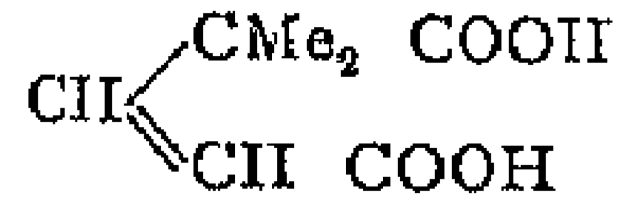
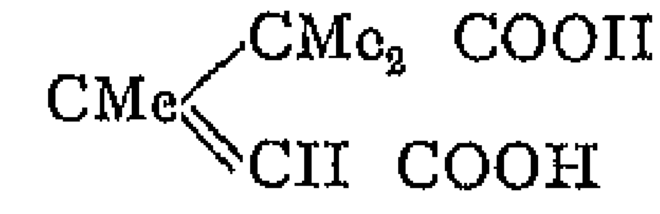


Eugenol   Isoeugenol

Glutaconic Acids.—Under the heading of triads are included glutaconic acid, HOOC $\overline{CH_2 \cdot CH}$ $\overrightarrow{CH}$ COOH, and its derivatives which have been extensively investigated by Thorpe and his co-workers.[1] Compounds of this type which contain mobile hydrogen furnish interesting examples of three carbon tautomerism accompanied by geometrical isomerism. In the case of the unsubstituted acid, the migration of a hydrogen atom leaves the molecular structure unchanged, although as has been pointed out by Packer and Thorpe,[2] the movement may or may not be accompanied by some interconversion of the *cis*- and *trans*-configurations, depending upon the spatial arrangement of the CH_2COOH group at the moment of transfer.

The arrangement of the constituent atoms in space is assumed to be governed by the tendency for similar groups to take up positions as remote as possible from one another. Such a tendency in the above acids can be satisfied owing to the power of free rotation about the single bond. It would thus be expected that the tautomeric change in the case of *trans* glutaconic acid would take place mainly without alteration in the stereochemical configuration but that the *cis*-acid would be largely converted into the *trans* form.

In compounds such as $\alpha\alpha$-dimethyl glutaconic acid (I) and $\alpha\alpha\beta$-trimethyl glutaconic acid (II), the last mobile hydrogen atom has been

I.    II 

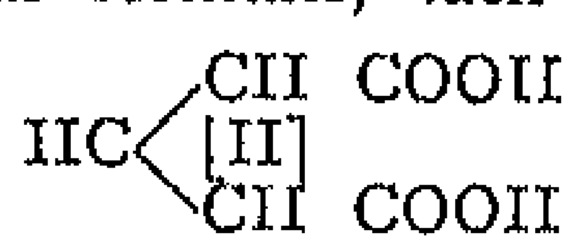
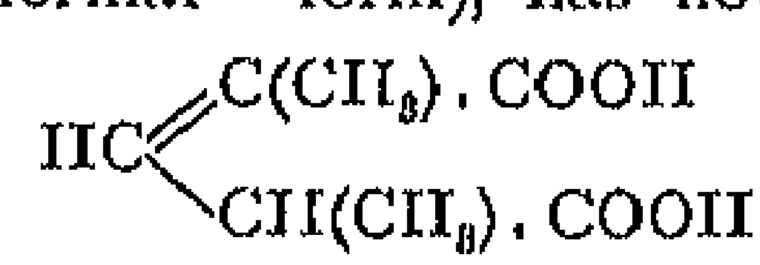
[1] *J. C. S.*, 1905, 87, 1669; Thorpe and Thole, *J. C. S.*, 1911, 99, 2187; Goss, Ingold and Thorpe, *J. C. S.*, 1923, 123, 327. [2] J. Packer and J. F. Thorpe, *J. C. S.*, 1926, 1199.

replaced by an alkyl group These acids only exist in the usual *cis*- and *trans*-isomerides, of which the former alone yield anhydrides Ordinary glutaconic acid, although of the *trans* type, also yields an anhydride The latter, however, presumably corresponds to the *cis*-acid, as on treatment with cold water it is converted into the very unstable *cis*-glutaconic acid[1] Anhydride formation is here due to the mobility of the glutaconic structure and is apparently preceded by isomerisation into the *cis*-acid

Tautomerism plays a more definite part in the case of alkyl substituted acids containing mobile hydrogen Although many of these also exist in two modifications, the isomerism is not that of the ordinary geometrical type Thorpe and Thole therefore suggested that the compounds are mobile tautomeric substances in which the α- and γ-carbon atoms function equally Support for this view is given by the work of Feist,[2] who found that the ozonides of unsymmetrically substituted esters of glutaconic acid decomposed to give *four* products, two corresponding to each of the two possible positions of the double bond, instead of yielding the *two* products to be expected from a static compound with the double bond in a fixed position The changes may be illustrated by the case of β-phenyl-α-methyl-glutaconic ester which on ozonisation gave a mixture of the esters of benzoyl-acetic, pyruvic, glyoxylic and α-benzoyl-propionic acids

$$\begin{array}{l} EtOOC\ CH_2\ C(C_6H_5)\ C(CH_3)\ COOEt \rightarrow C_6H_5\ CO\ CH_2\ COOEt + CH_3\ CO\ COOEt \\ \qquad\qquad\quad \uparrow\downarrow \\ EtOOC\ CH\ C(C_6H_5)\ CH(CH_3)\ COOEt \rightarrow O\ CH\ COOEt + C_6H_5\ CO\ CH(CH_3)\ COOEt \end{array}$$

Hence there is a symmetry about the molecule of glutaconic acid which is not conveyed in the usual formula with a fixed double bond The earlier suggestion that the stable acids were represented by symmetrical formulæ, such as III ("normal" form), has now been

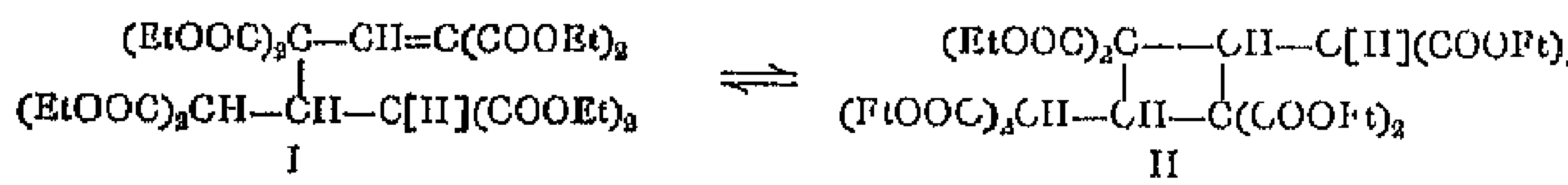
III    IV 

negatived by the resolution of $\alpha\gamma$-dimethyl glutaconic acid (IV) into optically active components[3] Such a resolution could not have been effected had the molecular structure been of the symmetrical "normal" type, although it is possible that the latter form may exist as an ephemeral intermediate phase

Ring-chain Tautomerism —Thorpe and Ingold conclude that in every triad system tautomerism may occur between open-chain and cyclic forms, *e g*

[1] Malachowski, *Ber*, 1929, 62, 1323 [2] Feist, *Ann*, 1922, 428, 25-75 [3] F H. McCombs, J Packer and J F Thorpe, *J C S*, 1931, 547

As an example of this type of change we may mention the esters I and II (prepared from ethyl α-carboxy-glutaconate, $(EtOOC)_2CH\cdot CH:CH\cdot COOEt$, by treatment with piperidine)[1] Both isomerides have



been isolated in the pure state, and the equilibrium is readily followed in solution

An interesting case of ring chain tautomerism which illustrates the influence exerted by different alkyl radicals[2] is that of the acids,

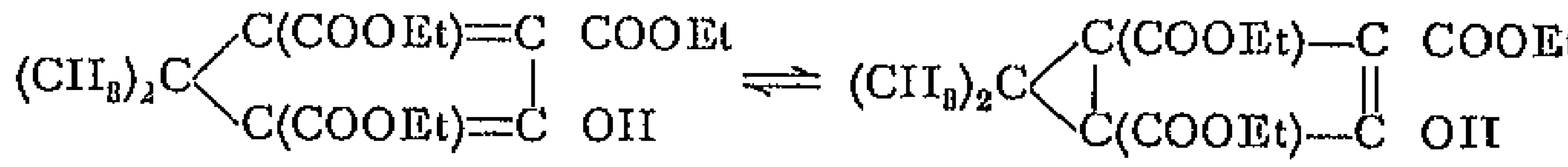
Equilibrium occurs in the presence of concentrated aqueous alkali (64 per cent), and the proportions of the two forms found in the mixture vary strongly with the volume of the groups R The influence of the latter is in agreement with Thorpe and Ingold's valency deflexion hypothesis (p 51) according to which an increasing bulk in the *gem*-dialkyl group (*e g* on passing from $Me_2C<$ to $Et_2C<$) results in the remaining two carbon valencies being forced closer together, thus tending to stabilise the cyclic form by relieving the internal strain in the cyclopropane ring

Series	Per cent Cyclic hydroxy-acid	Per cent Ketonic acid
$H, H > C <$	0	100
$CH_3, CH_3 > C <$	0	100
$CH_2—CH_2, CH_2—CH_2 > C <$ (ring)	0	100
$C_2H_5, C_2H_5 > C <$	62	38
$C_3H_7, C_3H_7 > C <$	71	29
$CH_2 < (CH_2—CH_2)_2 > C <$	100	0

Intra-annular tautomerism occurs when an equilibrium exists between two cyclic isomerides with or without the migration of an atom

[1] Ingold, Perren and Thorpe, *J. C S*, **1922**, 1765 [2] Deshapande and Thorpe, *J C S*, **1922**, 1430, Thorpe and Ingold, *Quelque Nouveaux Aspects de la Tautomerie*, p 28 (*Bull Soc Chim*, 1923), also *J C. S*, 1923, **123**, 113, 1206, 1683

of hydrogen. An example of the latter type is furnished by the cyclopentadiene derivatives[1] of the following structure:



(2) *Keto-enol System*, $\overleftarrow{C{=}C{-}OH}$. This includes acetoacetic ester (which is fully discussed on p. 261 *et seq.*) and many of the well-known examples of tautomerism, the equilibrium here occurring between the forms CH—C=O and C=C—OH.

$$\underset{\text{Keto form}}{CH_3 \cdot CO \cdot CH_2 \cdot COOEt} \rightleftharpoons \underset{\text{Enol form}}{CH_3 \cdot C(OH){:}CH \cdot COOEt}$$

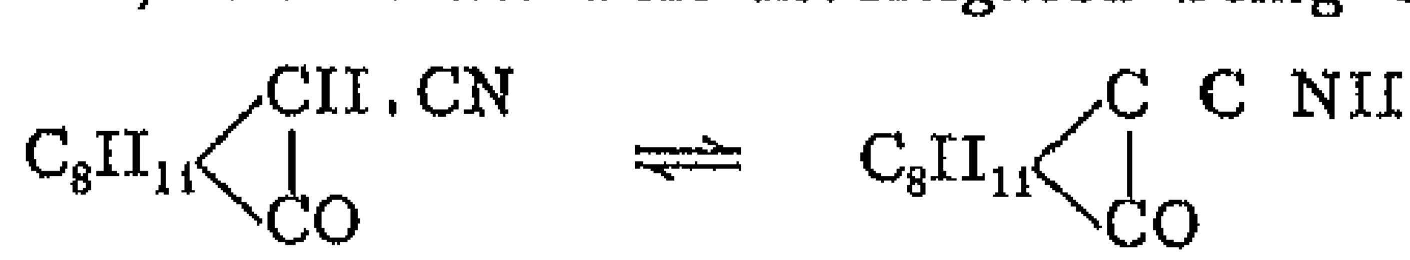
In addition to other β-ketonic esters, this group includes various 1 : 3-diketones, such as acetyl-acetone, $CH_3 \cdot CO \cdot CH_2 \cdot CO \cdot CH_3$, malonic ester, cyanacetic ester, and many cyclic derivatives which exhibit the properties of both ketones and hydroxy compounds, *e.g.* phloroglucinol (p. 419), resorcinol (p. 418) and camphor (p. 477).

(3) *Diazoamino System*, $\overleftarrow{N{=}N{-}NH}$. When diazobenzene chloride is allowed to react with *p*-toluidine the product is identical with that obtained from the interaction of *p*-diazotoluene and aniline, although on the ordinary formulation two different products would have been expected.[2]

$$\left.\begin{array}{l} C_6H_5 \cdot N{:}N \cdot Cl + H_2N \cdot C_6H_4 \cdot CH_3 = C_6H_5N{:}N \cdot NH \cdot C_6H_4 \cdot CH_3 \quad (a) \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \uparrow\downarrow \\ CH_3 \cdot C_6H_4 \cdot N{:}N \cdot Cl + H_2N \cdot C_6H_5 = CH_3 \cdot C_6H_4 \cdot N{:}N \cdot NH \cdot C_6H_5 \quad (b) \end{array}\right\} A$$

The two end-products are therefore represented as tautomeric forms in equilibrium with one another. This view is supported by the fact that when the double bond is disrupted by reduction or hydrolysis, *four* products are obtained, two corresponding to each of the theoretically possible forms.[3] (Compare three-carbon system, p. 67.) For example, the above product A gives on reduction a mixture of aniline, and *p*-tolylhydrazine (from *a*) together with *p*-toluidine and phenylhydrazine (from *b*).

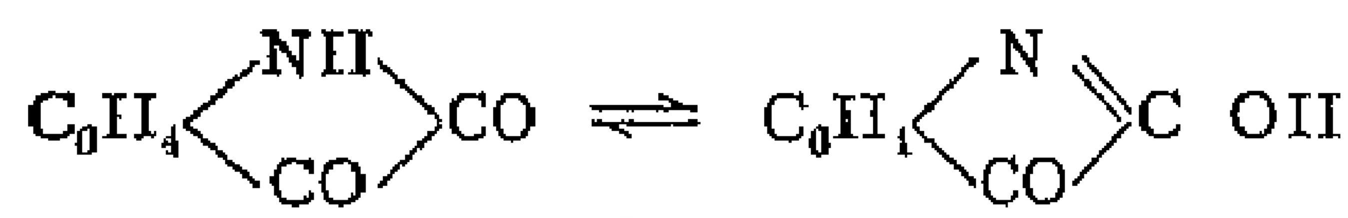
(4) *Cyanide-Imide System*, $\overleftarrow{C{=}C{=}NH}$. Few examples of this group are known, one of the best investigated being cyanocamphor:[4]



which has been isolated in two interconvertible forms.

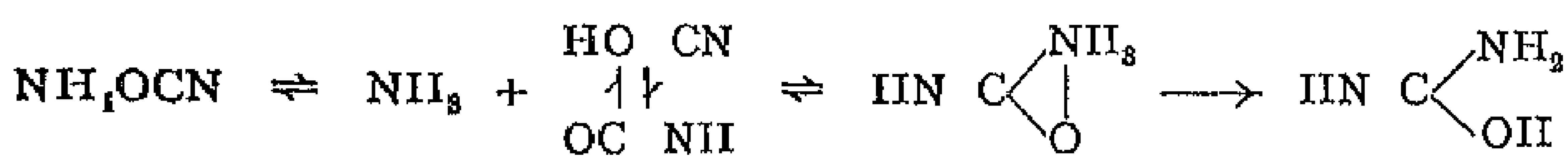
[1] W. H. Perkin and J. F. Thorpe, *J. C. S.*, 1901, 79, 729. See also *Ann. Rep. Chem. Soc.*, 1927, 117. [2] Meldola and Streatfield, *J. C. S.*, 1887, 51, 102, 434. [3] Noelting and Binder, *Ber.*, 1887, 20, 3004. [4] Hantzsch and Osswald, *Ber.*, 1889, 32, 641.

(5) The *Amido-Imidol System*, $\overleftarrow{N{=}C{-}OH}$, involves an equilibrium between the two structures $\underset{|\quad|}{N{=}C}{-}OH$ and $H\underset{|\quad|}{N{-}C}{=}O$ Compounds of this kind have long been known in isatin, indoxyl and oxindole (see index)



Isatin

Another example is cyanic acid, which according to E A Werner[1] represents an equilibrium mixture of the same type, the conversion of ammonium cyanate into urea being formulated as follows —



Werner also regards urea as exhibiting similar tautomerism

(6) *Amidine System*, $\overleftarrow{N{=}C{=}NH}$ A simple example of this triad system is cyanamide,[2] which is probably an equilibrium mixture of the type $N\vdots C\cdot NH_2 \rightleftharpoons HN:C:NH$ The unsymmetrical formula is supported by the formation of cyanamide from cyanogen chloride and ammonia, $CN\cdot Cl + NH_3 \longrightarrow CN\cdot NH_2 + HCl$ Cyanamide yields two isomeric series of alkyl derivatives, pointing to an alternative structure Diethylcyanamide on hydrolysis with acids decomposes into diethylamine, ammonia and carbon dioxide It is therefore formulated as $N\vdots C\cdot NEt_2$

$$N\vdots C\cdot NEt_2 + 2H_2O = NH_3 + CO_2 + HNEt_2$$

The diphenyl derivative, diphenyl carbodiimide, on the other hand, yields under the same treatment aniline and carbon dioxide, and is assigned the symmetrical structure

$$C_6H_5\cdot N:C:N\cdot C_6H_5 + 2H_2O = 2C_6H_5\cdot NH_2 + CO_2$$

Tautomerism of this kind was early discovered among the amidines by von Pechmann[3]

[1] *J. C. S.*, 1913, 103, 1010, 2275; 1914, 105, 923; 1915, 107, 715; 1918, 113, 694; 1919, 115, 1093 [2] E. A. Werner, *J. C. S.*, 1915, 107, 715 [3] *Ber.*, 1895, 28, 869, 2392; 1897, 30, 1779, 1783

Polymerism.

Compounds have the same percentage composition (*i e*, same empirical formula), but have different molecular weights and different properties.

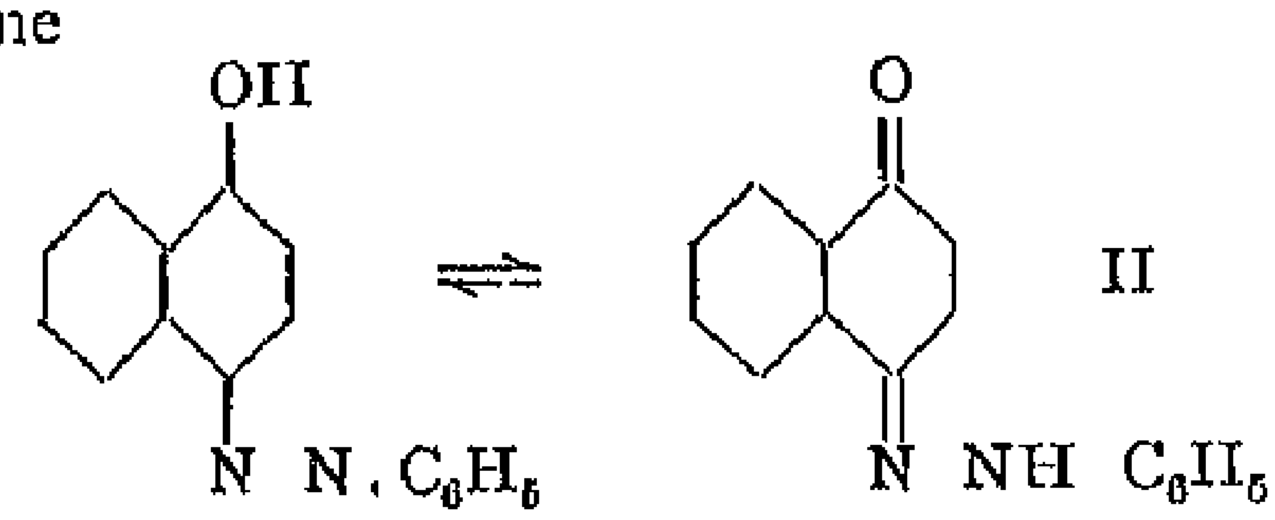
Isomerism.

Compounds have the same percentage composition and same molecular weight (*i e.*, same molecular formula), but have different properties

Isomerism

- Differences due to the *method of linking* of the atoms.
  - *Structural Isomerism.*
    - Different structure of the carbon chain or nucleus.
      - *Chain or Nuclear isomerism.*
    - Different positions of substituting groups on the same carbon nucleus or chain.
      - *Position-isomerism.*
    - Different radicals attached to a polyvalent atom.
      - *Meta-merism*
    - The isomerides differ only by the position of a hydrogen atom in the molecule, and are characterised by a tendency to undergo mutual isomerisation
      - *Tautomerism* or *Dynamic isomerism*
- Differences due to the *spatial position* of the atoms.
  - *Stereoisomerism*
    - The isomerides differ in optical activity
      - *Optical or mirror-image isomerism*
    - The isomerides are optically inactive and differ in all physical and many chemical properties
      - *Geometrical isomerism*

(7) *Azo-Hydrazone System*, $\overleftarrow{\mathrm{C{=}N{-}NH}}$ Laar[1] pointed out that the product (I) obtained by the interaction of diazobenzene chloride and naphthol is identical with (II) prepared from phenylhydrazine and α-naphthoquinone

I  II

Probably there is actually an equilibrium between the two possible forms, one of which is so unstable as to disappear in the final product

Similarly R Meyer found that when diazobenzene chloride is combined with sodio-malonic ester and the product hydrolysed, the substance obtained is identical with that prepared from phenylhydrazine and mesoxalic acid It may therefore be represented either as a

$$C_6H_5\,N_2\,Cl + NaCH(COOEt)_2 \longrightarrow C_6H_5\,N\,N\,CH(COOH)_2 \quad \text{III}$$
$$C_6H_5\,NH\,NH_2 + O\,C(COOH)_2 \longrightarrow C_6H_5\,NH\,N\,C(COOH)_2 \quad \text{IV}$$

hydrazone IV, or as an azo-compound III

(8) *Nitro-Pseudonitro System*, $\overleftarrow{\mathrm{C{=}N{-}OH}}$ (with $\|$ O on N) This type of isomerism is exhibited by primary and secondary nitro compounds and is fully discussed on p 156

$$C_6H_5\,CH_2\,N{\overset{O}{\underset{O}{\lessgtr}}} \quad \rightleftarrows \quad C_6H_5\,CH{=}N{\overset{OH}{\underset{O}{\lessgtr}}}$$

PHYSICAL PROPERTIES OF ORGANIC COMPOUNDS[2]

In respect of physical properties there is no general difference to be traced between carbon compounds and those of other elements

In modern times the investigation of physical properties has become of great importance in the study of organic compounds, being of value not only for the purpose of identification but also as a means of attacking the problem of molecular constitution

1. Colour[3]

Among those properties which make their appeal directly to the senses that of colour stands out prominently. Some organic compounds possess colour and others are colourless A careful distinction, however,

[1] *Ber*, 1885, 18, 648 [2] Compare Smiles, *Relations between Chemical Constitution and Physical Properties* (Longmans). [3] See also Cohen, *Organic Chemistry*, Part II (Arnold), and Kauffmann, *Ueber den Zusammenhang zwischen Farbe und Constitution bei chemischen Verbindungen* (Ahrens Sammlung, vol ix, 1904 Also vol xii)

must be drawn between colour and the ability to function as a dye. A compound may be strongly coloured and yet have no power, even with the aid of a mordant, to fix itself on the fibres of cotton, wool or silk.

Despite much experimental investigation from various quarters, the problem of the relation between colour and constitution is still unsolved. One of the main difficulties lies in the complexity of all the contributory factors. So far, no clear insight has even been obtained into the purely physical processes on which the phenomenon of colour depends, although it is known that the appearance of colour in a compound is connected with its power of absorbing rays of certain wave-lengths. For a proper understanding of the relationship between colour and constitution we also require to know more about the inner structure and state of vibration of the molecule. At present all that can be said is that a number of regularities have been discovered bearing upon this point.

It appears from numerous researches, carried out for the most part within the last twenty years, that double bonds of practically any kind are the primary cause of colour. Apart from their mere presence, the position they occupy within the molecule also plays an important rôle. Following a suggestion of Witt,[1] the term **chromophore** has been applied to all those groups which give rise to colour when allied in suitable manner and sufficient number with hydrocarbon radicals. In general, however, the full development of colour is not attained in combination with hydrocarbon radicals alone, but only when the influence of the chromophore is strengthened by the presence of certain other groups, which Witt calls **auxochromes**. The most important chromophores are the groups

C=C,	C=O,	C=N,	N=N,	N_2O,	N=O
	Carbonyl,		Azo,	Azoxy-,	Nitroso group

Among coloured hydrocarbons may be mentioned fulvene,[2] which contains three of the groups C=C. The presence of one or even of two such groups does not result in the production of any colour. Another comparatively weak chromophore is the carbonyl group. Colour is first noticeable in the presence of two of these, and then only if they are in very close proximity to one another. Thus diacetyl, $CH_3 \cdot CO \cdot CO \cdot CH_3$, with two carbonyl groups adjacent to one another, is a yellow liquid. The azo group, on the other hand, is one of the strongest chromophores, even so simple a compound as diazomethane, $CH_2\langle\begin{smallmatrix}N\\ \|\\ N\end{smallmatrix}$, being yellow, whilst azobenzene, $C_6H_5-N=N-C_6H_5$, forms orange-red crystals. Another strong chromophore is the nitroso group, the true nitroso compounds being coloured an intense blue or green in the liquid state or in solution.

The physicist Hartley found that benzene and many of its colourless derivatives show an absorption spectrum with the short ultra-violet rays, and are therefore coloured in the wider sense of the term. In his opinion each benzene derivative may be converted into a coloured substance by

[1] Witt, *Ber.*, 1876, 9, 522. [2] Thiele, *Ber.*, 1900, 33, 666.

chemical changes, which result in the displacement of one or more absorption bands into the visible part of the spectrum. This is achieved by introducing atomic complexes into the benzene ring which damp its natural period of vibration. These views were also accepted by Baeyer, who, however, did not consider the damping of the oscillations to be the sole cause of the appearance of colour.

The term chromophore has thus gradually acquired a new meaning as a result of recent research. The production of colour is believed to be due, not so much to the presence of certain combinations of atoms, as to the secondary influence they exert on the molecule in displacing its period of oscillation into the visible part of the spectrum. Coloured compounds have also been discovered possessing none of the so-called chromophore groups. In general, coloured compounds are those in which the atomic arrangement so modifies the vibration of the molecule as to produce an absorption band in the visible part of the spectrum.

The auxochromes, the most important of which are the amino-group (NH_2) and the hydroxyl group (OH), may act in two ways. On the one hand they may, by their presence, endow a substance with the capacity for salt formation, with the possible production of a dye-stuff, and on the other, their introduction may lead to a deepening and intensification of the original colour. Those compounds containing a chromophore group, in which the entrance of an auxochrome produces a more strongly coloured substance or dye-stuff, are termed *chromogenes* by Witt.

In many cases the sharp distinction implied in the separation of groups into chromophores and auxochromes is scarcely justified, since the latter may be able to function as the former in calling forth the characteristic colour.[1]

It will be noticed over and over again in connection with the discussion of coloured substances and dye-stuffs, that there is a strong tendency to associate colour with the presence of double bonds and in particular of a quinonoid structure in the molecule.

The suggestion frequently advanced, that colourless substances may develop colour by simply passing into the ionic state, has been definitely disproved by Hantzsch. The colour of a compound is independent of the presence or absence of ions.

Phototropy[2] is the property possessed by some substances of changing colour according to the intensity and wave length of the incident light. It has been thoroughly investigated in the case of the fulgides by Stobbe.

That the colour of solid matter varies continuously with the temperature has frequently been observed with organic compounds. The backward and forward continuity of the colour alteration is a special characteristic of this kind of reversible change. Stobbe, by

[1] Hantzsch, *Ber.*, 1906, 39, 1091. [2] Stobbe, *Ann.*, 1908, 359, 1; *Ber.*, 1913, 46, 1226.

whom this phenomenon has also been examined in the case of the fulgides,[1] has described such compounds as *thermochromatic*

For a discussion of the property of fluorescence, see Cohen, *Organic Chemistry*, Part II (Arnold)

2 State of Aggregation of Organic Compounds, Crystallisation

Comparatively few organic compounds are gaseous at the ordinary temperature, the majority of them exist normally in the liquid or solid state In the latter case they may be amorphous or crystalline Of these, the amorphous substances approximate more closely to liquids in their molecular condition, and their manipulation in the laboratory offers much greater difficulty than that of crystalline compounds The crystalline form of an organic compound is often an important criterion of its identity

To purify a substance by crystallisation, it is usually dissolved by heating with a suitable solvent, filtered from any undissolved impurities and the warm solution allowed to cool The greater part of the dissolved material then separates in the crystalline state, while the small impurities remain dissolved in the mother liquor Crystallisation is also employed for separating the individual constituents of a mixture from one another (*fractional crystallisation*) In some cases the organic substance may separate in the form of an addition compound with the solvent.

Many carbon compounds have the property of crystallising in two or more distinct forms, a phenomenon known as dimorphism or polymorphism Hexachloroethane, for example, may separate in crystals belonging to the rhombic, triclinic or cubic system

Comparatively little is yet known as to the relation between chemical constitution and the crystal form of organic compounds It has been established, however, that a definite connection exists between symmetry and asymmetry in molecule and crystal, and that changes in the chemical structure of the molecule also affect the conformation of the crystal Asymmetry has already been discussed in dealing with the stereoisomerism of asymmetric carbon compounds (p 33) The two stereoisomerides may differ in their configurations in such a way that they appear as enantiomorphous mirror-images of one another Corresponding to this we find a similar enantiomorphous difference in their crystal forms

3. Melting-point

Under the influence of heat, solid compounds generally change their state of aggregation and become fluid In many cases, however, chemical change takes place, followed by decomposition and the formation of new compounds Those substances that are fusible without decomposition possess a definite melting-point At this point the solid and liquid forms of a body are in equilibrium with one another, the melting-point therefore coincides with the freezing-point

[1] Stobbe, *Ann*, 1911, 380, 17

The melting-point is one of the most important physical constants of an organic compound In the vast majority of cases it is used for the identification of a substance and gives, in addition, valuable information as to the state of purity While small impurities often bring about a considerable depression of the melting-point, larger amounts cause irregular and protracted melting, so that it is no longer possible to determine the point with certainty Phenanthraquinone, for example, melts at 206°, 2-chlorophenanthraquinone at 236°, but a mixture of the two in equal portions melts indefinitely between 160° and 190°

The melting-point is usually determined in an apparatus such as that illustrated in Fig 16 or by use of a beaker provided with a glass stirrer A few milligrams of the dry, finely powdered substance are contained in a capillary tube, closed at its lower end and made to adhere to the stem of a thermometer which is immersed in castor oil or strong sulphuric acid Unless the melting-point is quoted as "uncorrected," a correction should be made for the portion of the mercury thread of the thermometer which is not immersed in the liquid

FIG. 16.

The melting point of successive members of a homologous series rises gradually with increase of molecular weight, but this is often accompanied by a minor alternation of rise and fall throughout the series Members with an uneven number of carbon atoms have frequently a lower melting point than the preceding compound containing one carbon atom less

Among structurally isomeric compounds, that which is most symmetrically built usually has the highest melting point Thus of the isomeric di substituted derivatives of benzene, the para compound melts higher than the ortho- or meta compounds

A knowledge of the *melting-points of mixtures* is of special interest to the practical worker At a certain composition the melting-point of a mixture of two substances reaches a minimum which lies below the melting-point of either of the two constituents Two substances are therefore identical when a mixture of the two in any proportions has the same melting-point as either of the pure substances The melting-point and composition of a mixture of substances is changed by repeated recrystallisation, and hence the constancy of the melting-point under this treatment is strong proof of the homogeneity and purity of the starting material

4. Boiling-point and Distillation.

The boiling-point of a liquid possesses the same importance as the melting-point of a solid, and is of great utility in the recognition, separation and purification of those compounds which are volatile without decomposition

In most cases the boiling-point is determined by the same process of distillation which serves for its purification and isolation A

distillation flask (see Fig. 17) is about two-thirds filled with the liquid, and closed by a cork bearing a thermometer, the bulb of which should be a little below the side tube of the flask. In dealing with easily volatile substances the side tube is usually connected to a condenser. When the liquid is heated to boiling-point, the vapours escaping through the side tube heat the thermometer bulb on their way and are again cooled to the liquid form in the condenser. The contents of the flask are boiled vigorously, and if the liquid is homogeneous the thermometer remains steady throughout the whole period of distillation at a temperature representing the boiling-point. If desired, a correction may be made for that part of the thermometer thread not heated by the vapour, and should the barometric pressure be other than 760 mm. it should be noted, or a correction applied.

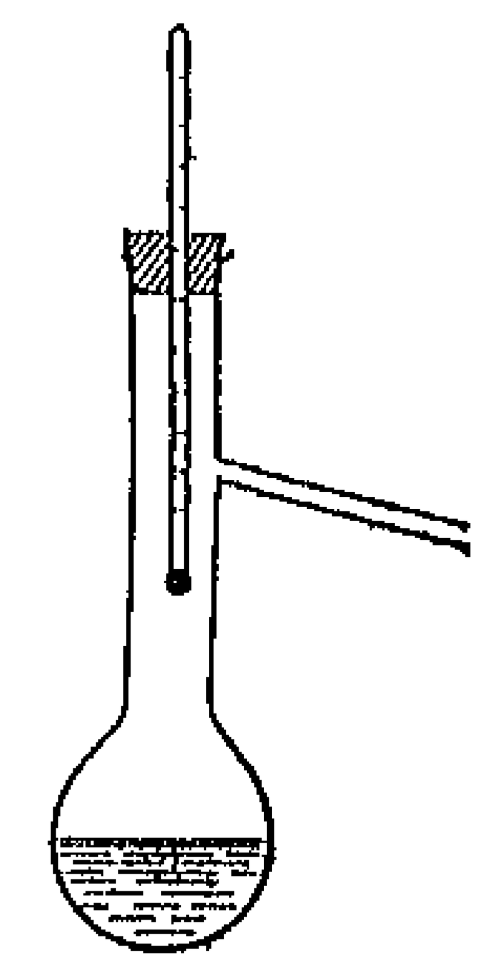


FIG. 17

Many substances which cannot be distilled under ordinary barometric pressure owing to decomposition, may be safely distilled under diminished pressure. In this case the internal pressure must be quoted with the boiling-point. Distillation under diminished pressure is a most valuable means for the isolation and purification of high-boiling compounds, and plays an important rôle in laboratory as well as in technical work.

A further form of distillation, frequently employed in the separation and purification of compounds sparingly soluble in water, is distillation in steam. Many such compounds, even those of high boiling-point or which cannot be distilled alone without decomposition, volatilise more or less easily when heated with water, or when steam is blown through the mixture. The boiling-point of a mixture of two liquids, which do not dissolve one another, is attained when the sum of their respective vapour pressures is equal to the external (atmospheric) pressure. When this is the case both liquids distil. Since water is generally by far the more volatile of the two, it follows that the other liquid distils at a temperature much below its normal boiling-point. Steam distillation, therefore, is merely a special case of distillation under diminished pressure.

In order to isolate the individual constituents from a mixture of volatile compounds we make use of fractional distillation. This serves as a means of separation when there is a sufficient difference between the respective boiling-points of the constituents. Only if the boiling-points of two liquids lie far apart is it possible to attain a comparatively complete separation in one distillation. In this case the lower boiling compound comes over first at an approximately constant temperature, which then rises rapidly to the boiling-point of the less volatile compound, this finally distilling over pure. Generally speaking, however, it is not possible to obtain even an approximate separation in

this way by a single distillation, and the process must be repeated several times The efficiency of the operation is greatly increased by making use of a device known as a fractionating head (as designed by Wurtz, Hempel, Young and others) which brings about a partial condensation of the escaping vapour, returning the liquid so formed to the distillation vessel In technical work a similar principle is adopted in "fractionating columns" (and dephlegmators), such as are described later under the purification of alcohols and benzene hydrocarbons

Kopp was the first to point out the relationship existing between the constitution and boiling-point of an organic compound, and although the laws derived by him have not proved generally applicable, they nevertheless gave rise to a number of other fruitful investigations on the subject

In a homologous series the boiling-point usually rises from member to member with increase in molecular weight In the case of the normal primary alcohols, for example, the boiling-point rises at first fairly regularly by 18° to 22° for each additional CH_2 in the molecule This increase gradually diminishes as we pass up the series With the mixed aromatic hydrocarbons, the entrance of a CH_3 group into the side chain produces the same difference in boiling-point as with the homologues of the fatty series, *i e*, about 18° to 22°, the entrance of a CH_3 group into the benzene ring, however, raises the boiling-point about 30°

Regularities may also be traced between the boiling-points of compounds which do not belong to the same homologous series, but show a definite structural relationship to one another Thus an organic acid is commonly found to boil about 40° higher than the corresponding primary alcohol, and about 45° higher than its ethyl ester

The boiling-points of the corresponding normal hydrocarbons of the series C_nH_{2n+2}, C_nH_{2n}, and C_nH_{2n-2} approximate closely to one another (*e g.*, $C_{18}H_{38}$, 181·5°, $C_{18}H_{36}$, 179°, $C_{18}H_{34}$, 184°)

In the case of isomeric substances which differ in the construction of their carbon chains, the highest boiling-point corresponds to the normal structure in which no side chains are present As soon as side chains appear the boiling-point is lowered, and the more branched the carbon chain the greater is the difference observed

Among regularities in the aromatic series it may be mentioned that ortho-substitution products generally have somewhat higher boiling-points than the isomeric meta- and para-compounds

5 Solubility

Many carbon compounds are more or less readily soluble in water, for such as are not we may employ as solvents alcohol, ether, ligroin (petroleum ether), glacial acetic acid or benzene, as well as mixtures

of these liquids A selected solvent is frequently utilised in the identification, isolation or purification of a compound Hydrocarbons are either insoluble or very sparingly soluble in water, but if hydrogen in these compounds is replaced by oxygen or the hydroxyl group the solubility increases, and becomes the greater as more hydrogen is substituted The first members of the homologous series of alcohols, aldehydes, ketones and acids are soluble in water, but as the proportion of carbon increases the solubility in water diminishes

6 Density or Specific Gravity

It has already been pointed out that a simple relationship exists between the density and molecular weight of a gaseous compound (p 13) Some regularities have also been discovered for liquid substances in connection with their molecular volume, *i e*, molecular weight divided by specific gravity For further information on this subject reference should be made to papers published by Traube[1]

7 The Parachor[2]

For many years chemists have sought to discover an additive property of compounds which could be measured accurately and which would be independent of the temperature, the object being to make use of the values so found to obtain an insight into the constitution of the molecules Partially successful attempts of this nature were made, for example, by Kopp, in measuring the molecular volumes of liquids at their boiling-points instead of at atmospheric pressure Recently, a function applying to non-associated liquids has been investigated by Sugden, who make use of the value [P], termed the *parachor*, calculated from the expression $[P] = M\gamma^{\frac{1}{4}}/(D-d)$, in which M represents the molecular weight, γ the surface tension, D the density of the liquid substance and d the density of the vapour As has been pointed out by Lowry, this function is of the nature of a molecular volume, M/D, "which has been corrected with the help of the surface tension for the overwhelming influence of an internal pressure ranging in typical cases from 1500 to 60,000 atmospheres" The value is thus made independent of the temperature at which it is measured[3]

Atomic Constants—By comparing the values of the parachor for successive members of a homologous series Sugden found a mean constant difference for CH_2 amounting to 39 0 From this it is possible to calculate the parachor for carbon and hydrogen For example, the parachor for propane, C_3H_8, was found to be 150 8, hence by subtracting $3\times CH_2 = 117$, it is evident that $2H = 33$ 8 From a number of similar determinations the average value of 2H was found to be 34 3,

[1] Traube, *Ahrens Vorträge*, 1899, 4, 255 See also Cohen, *Organic Chemistry*, Part II (Arnold) [2] *The Parachor and Valency*, by Sugden (Routledge, 1930) [3] Lowry, *Nature* 1930, p 365

whence H = 17 1. This is in good agreement with that found for liquid hydrogen, H_2 = 35 1 The value for carbon, C = 4 8, is deduced from $CH_2 - H_2$ Other elements are calculated in a similar way from the parachors of *saturated* aliphatic compounds, the parachor for chlorine, for example, being obtained from the difference between $CHCl_3$ and CCl_4 By comparing saturated compounds in this manner Sugden derived a large number of constants characteristic of the different atoms

Structural Constants—In all saturated compounds the contribution of the single valency bond uniting the elements is assumed to be zero In Sugden's words, this means that the single bond is chosen as an arbitrary zero level from which the effect of other structures is measured On comparing saturated open chain hydrocarbons with those of unsaturated and cyclic types, it was found that a definite contribution to the parachor is made by each double bond, triple bond and each 3-, 4-, 5-, or 6 membered ring present in the molecule The atomic and structural parachors thus deduced have been summarised by Sugden in the following table

Atomic and Structural Parachors

C	4 8	Triple bond	46 6
H	17 1	Double bond	23 2
N	12 5	3 Membered ring	16 7
P	37 7	4 „ „	11 6
O	20 0	5 „ „	8 5
S	48 2	6 „ „	6 1
F	25 7	O_2 in esters	60 0
Cl	54 3	Semipolar double bond	− 1 6
Br	68 0		
I	91 0		

It is interesting to note that the same value for the double bond is obtained whatever the nature of the atoms linked together, thus the double bonds in ethylene, acetone, carbon bisulphide (2) and nitrosyl chloride all approximate to 23 2 and the same value is given irrespective of whether the double bonds are conjugated or widely separated It will be observed that the parachor for the triple bond is almost exactly double that of the double bond, consequently it does not serve to distinguish between compounds such as CH_3O C N and CH_3 N C O The parachor is thus a function of a very simple type, which is made up of two series of constants, one set for the atoms and another for the linkages present in the molecule

The parachor provided the first experimental evidence in support of Lowry's view that a double bond is not always a double covalence or a double electrovalence, but may in certain cases consist of an electrovalence superimposed on a covalence (see p 29) Sugden found that among compounds formerly written with a double bond, the great majority gave a value for the double linking of +23 In some compounds, however, a small negative value of − 1·6 had to be assumed

Further examination showed that the latter substances could only be formulated as containing a double covalence by breaking the Lewis octet rule and attributing to one of the atoms participating in the double bond a valency shell of ten or more electrons. In all such cases, one of the atoms still retains unshared electrons and it is possible to preserve the octet rule by formulating the double linking as a *semipolar* or mixed *double bond*. As an illustration of this point we may mention the case of trimethylamine oxide which is discussed on p. 30.

Among other compounds giving small negative values for the double bond and which are therefore supposed to contain one or more semipolar double bonds are thionyl chloride, phosphorus oxychloride, methyl sulphate, ethyl sulphite, sulphonic derivatives and nitro compounds.

$$Cl_3P \rightleftharpoons O \qquad (EtO)_2S \rightleftharpoons O \qquad (MeO)_2S(\rightleftharpoons O)_2 \qquad C_6H_5{-}N(\rightleftharpoons O)_2$$

On the other hand derivatives of carbonic acid, nitroso compounds and nitrites give the usual values corresponding to a non-polar double bond.

The measurement of parachor values leads to a number of conclusions of interest to organic chemists. The values for benzene derivatives, for example, are in excellent agreement with the Kekulé formula containing three normal double bonds.

C_6	6×4.8		= 28.8
H_6	6×17.1		= 102.6
3 double bonds	3×23.2		= 69.6
6 membered ring			= 6.1
[P] observed	206.2	[P] calculated	= 207.1

Azoxy-compounds have one double bond and one semipolar double bond, thus supporting the unsymmetrical formula for these compounds.

$$C_6H_5{-}N{=}N{-}C_6H_5 \atop \qquad\Downarrow O$$

A curious anomaly is found for the oxygen value in carboxylic esters, the parachor for which is slightly less than that calculated on the usual formula. This is part of the general abnormality of the carboxyl group for which no satisfactory explanation has yet been advanced.

Parachor measurements have recently been employed[1] as a means of determining the structure of isocyanides, the results supporting formula I in place of the bivalent carbon structure II, advanced by Nef.

$$\text{I}\quad R{-}N \stackrel{\rightarrow}{=} C \qquad\qquad \text{II}\quad R{-}N{=}C$$

8. Electrical Conductivity

Since the development of the dissociation theory the property of conductivity has been frequently utilised in organic chemistry, particularly for the solution of theoretical problems. Mention may

[1] D. L. Hammick, R. G. A. New, N. V. Sidgwick, and L. E. Sutton, *J. C. S.*, 1930, 1876.

be made of the work of Ostwald and Arrhenius on the conductivity of organic acids and their sodium salts, and the later investigations of Hantzsch on substances with labile groups

Determination of the Basicity of an Acid from the Electrical Conductivity of its Sodium Salt—According to Ostwald,[1] the conductivity of the sodium salt affords a means of deciding the basicity of an acid, since there is a definite relationship between the molecular conductivities of the alkali salts of mono-, di- and tribasic acids, between the dilutions of 32 and 1024 litres In the case of the sodium salt of a monobasic acid the molecular conductivity increases by 10 to 13 units between these dilutions, for a dibasic acid the increase is 19 to 25, and for a tribasic acid approximately 28 units These differences are so considerable that they may be used to distinguish between mono- and polybasic acids As most sodium salts are soluble in water, even when the free acids do not possess this property, the method is of great utility. It fails, however, if the acid is so weak that the salt is considerably hydrolysed in aqueous solution

Strength of Acids and Bases Influence of Substitution on the Dissociation of Acids[2]—The conductivity has been found to give a measure of the strengths of acids and bases in so far that the stronger acid or base is the better conductor On these grounds Arrhenius in 1884 suggested that the strength of an acid was proportional to its conductivity, or rather to its degree of dissociation A corresponding relationship also holds for bases

It has long been known that the strength of an acid such as acetic acid is increased when a hydrogen atom is replaced by chlorine Thus monochloroacetic acid, $CH_2Cl\ COOH$, is distinctly stronger than acetic acid, $CH_3\ COOH$, dichloroacetic acid, $CHCl_2\ COOH$, is stronger still, and trichloracetic acid, $CCl_3\ COOH$, even more so The same sequence is to be observed in the dissociation constants K, for which Hantzsch found the values

$CH_3\ COOH$	$CH_2Cl\ COOH$	$CHCl_2\ COOH$	$CCl_3\ COOH$
$1\ 80 \times 10^{-5}$	155×10^{-5}	$5{,}140 \times 10^{-5}$	$121{,}000 \times 10^{-5}$

A similar increase in acidity occurs when hydrogen is replaced by many other substituents, although methyl and amino groups diminish the value Different substituents affect the acid strength of acetic acid in the order $NO_2 > CN > COOH > Cl > Br > I > OCH_3 > H > CH_3$ In the case of benzoic acid substitution in the ortho position exerts a greater influence than in the meta or para position, and the above order of groups also holds approximately for the *o*-substituted acids The fundamental nature of the change following on substitution is

[1] *Z phys. Ch*, 1887, 1, 74, 1888, 2, 901, also Walden, *Z phys Ch*, 1887, 1, 529, 1888, 2, 49. [2] See also Flürscheim, *J C S*, 1909, 95, 718

shown by the fact that the same sequence of groups is often repeated in their relative effect on other properties These *polar* regularities are sometimes of value in solving problems of constitution

Unsaturated Acids—The presence of a double bond in an acid raises the acidic strength, *e g*, hexoic acid K = 00146, $\alpha\beta$ hexenic acid K = 00189, $\beta\gamma$ hexenic acid K = 00264, $\gamma\delta$ hexenic acid K = 00174, $\delta\epsilon$ hexenic acid K = 00191 The alternation in values as the double bond is moved away from the carboxyl group has been explained by Flurscheim[1] on the basis of a maximum disposable affinity for each atom, the distribution of which varies according to the other elements present and the manner in which they are united A double bond does not utilise the whole of the affinity corresponding to two valency bonds, and there is therefore a surplus to be distributed elsewhere This leads to an alternation of strong and weak links in the carbon chain as indicated in the formulæ

$$\text{I}\quad R\,CH\,CH—C\begin{matrix}\nearrow O\\ \searrow O—H\end{matrix}\qquad\qquad \text{II}\quad R\,CH\,CH—CH_2—C\begin{matrix}\nearrow O\\ \searrow O—H\end{matrix}$$

In I the ionisable hydrogen atom is more firmly united to oxygen than in II The latter compound will therefore ionise more readily and be the stronger acid.

A similar explanation has been applied to the influence of substituents

Hydrolysis—In aqueous solution the salt of a weak acid or base undergoes a partial decomposition termed hydrolysis A solution of aniline hydrochloride, for example, contains besides aniline hydrochloride a certain amount of free aniline and free acid, the latter of which is in addition subject to electrolytic dissociation These constituents of the solution exist in a state of equilibrium which varies with temperature and concentration In a similar manner a solution of sodium phenolate contains a proportion of free phenol and sodium hydroxide Water therefore possesses the property of partially liberating weak acids or bases from their salts The amount of hydrolysis may be determined quantitatively by conductivity measurements and a variety of other methods[2]

In a somewhat different sense the term *hydrolysis* is employed to indicate the decomposition of esters, amides, nitriles, etc, through the agency of water (see pp 147, 202, 205) Generally speaking, the reagents actually used in such cases are acids and alkalis which bring about the reaction with greater velocity and completeness

9 Polar Properties of Organic Compounds

Within the last few years considerable progress has been made in our knowledge of the electrical structure of compounds, more especially with reference to the changes produced by substitution It has long been usual to classify substituent groups as *electronegative* or *electropositive* in type, according to their influence upon the ionisation of acids and bases Electronegative groups, in general, increase the dissociation constant of an organic acid, whilst electropositive groups lower the value

[1] *J C S*, 1909, 95, 718 [2] See Findlay, *Practical Physical Chemistry* (Longmans)

But it is only recently that the work of Debye, J J Thomson and others has enabled us to give a precise and quantitative meaning to the polarity of substituent groups The present standpoint may be summarised briefly as follows

The electrical centre or centre of gravity of the electrons in a molecule may or may not coincide with that of the protons In the former case the molecule will be non-polar with respect to an external field, but in the latter case it will behave as an electrical doublet or *dipole* If we represent the molecule diagrammatically as in Fig 18, the positive and negative centres (or poles) may be indicated by + and − respectively, separated from one another by a distance d Obviously the molecules will have a definite turning moment in an electrical field and will tend to arrange themselves uniformly in such a manner as to produce a system of minimum potential energy, a tendency which will be opposed by the heat vibration of the molecules The magnitude of the turning moment depends upon e the charge at the poles and d their distance apart A quantitative measure of this function is given by the dipole moment, μ, which may be calculated by various methods from data referring to the refractivity and dielectric constant of the compound in the gaseous state or in dilute solution in a non-polar solvent such as benzene or hexane[1] As a result of many investigations on these lines it has been found that hydrocarbons in general have an electrical moment which is either zero or of very small magnitude Mono-substituted hydrocarbons, on the other hand, give values of μ which are characteristic of the particular substituent present and depend only in minor degree upon the nature of the hydrocarbon radical to which it is attached This is illustrated by the figures for derivatives of ethane and benzene given in table on p 85, in which the signs + and − are introduced solely for the purpose of indicating the electropositive or electronegative character of the polar substituent Further confirmation of the specific influence of the substituent is given by the work of K L Wolf[2] on various ketones and of Errera and Sherrill[3] on the isomeric heptanols

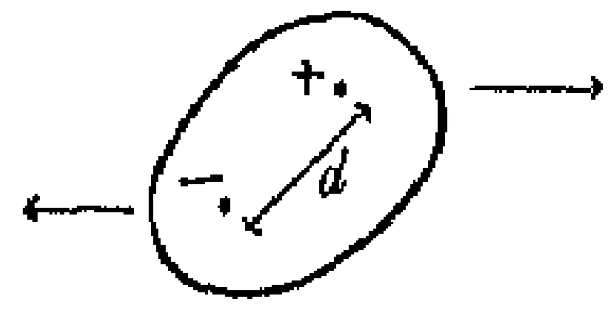


FIG 18.

It appears that in the majority of cases, at all events, the dipole is located within the substituent group or in the neighbourhood of the bond joining it to the adjacent carbon atom Among electronegative groupings[4] the positive end of the dipole is directed towards the parent

[1] The external field will also tend to distort the dipole to an extent depending on the strength of the field and the deformability of the molecule For further details reference should be made to *Polar Molecules*, by P. Debye (Chemical Catalogue Co, New York, 1928), Højendahl, Thesis (Copenhagen, 1928) [2] K L Wolf, *Zeit phys Chem*, 1929, B2 39 [3] Errera and Sherrill, *J A C S*, 1930, 52, 1993. [4] Probably many substituents are composite dipoles. The nitro-group, one of the most powerful polar groups, contains a semi-polar double bond (see p. 81), which results in the N and O atoms being respectively positively and negatively charged

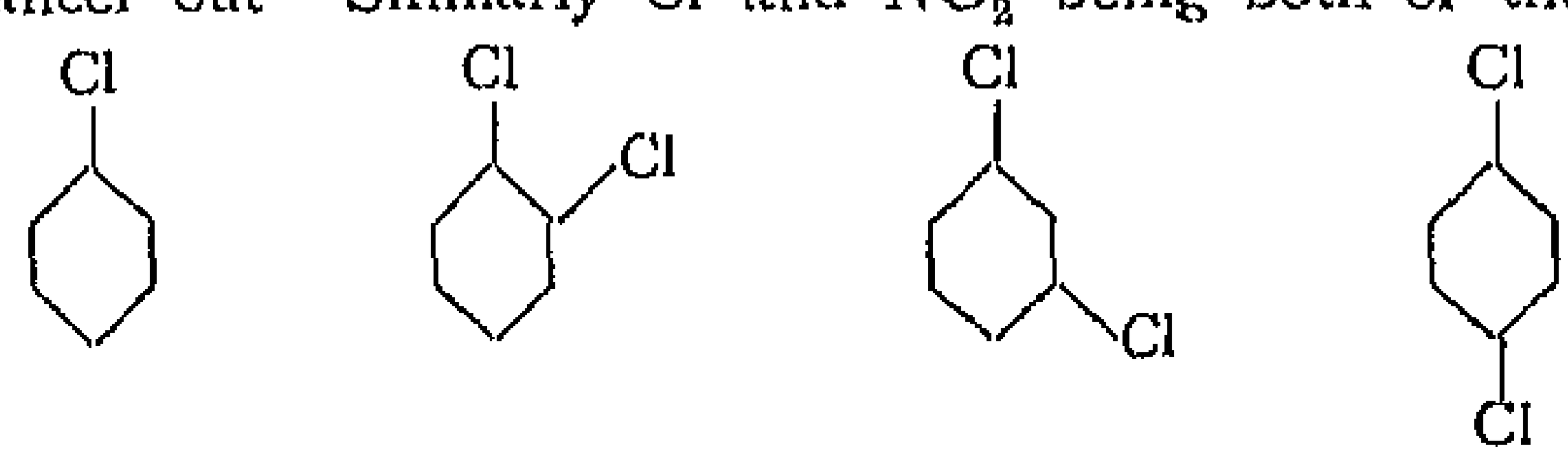
hydrocarbon radical, the reverse arrangement holding for electropositive groups

$$\overset{+}{H_3C}\ \overset{-}{Cl} \qquad \overset{+}{H_3C}\ \overset{-}{NO_2} \qquad \overset{-}{H_3C}\ \overset{+}{NH_2}$$

Dipole Moments of Compounds[1]

	$\mu \times 10^{18}$		$\mu \times 10^{18}$
$C_2H_5\ NH_2$	+ 1.31	$C_6H_5\ NH_2$	+ 1.5
(C_6H_{11})	0	$C_6H_5\ CH_3$	+ 0.4
$C_2H_5\ COOH$	− 0.6 (?)	C_6H_6	0
$C_2H_5\ O\ C_2H_5$	− 1.2	$C_6H_5\ COOH$	− 0.9 (?)
$C_2H_5\ OH$	− 1.7	$C_6H_5\ OCH_3$	− 1.2
$C_2H_5\ I$	− 1.7	$C_6H_5\ I$	− 1.25
$C_2H_5\ Br$	− 1.9	$C_6H_5\ Br$	− 1.5
$C_2H_5\ Cl$	− 2.0	$C_6H_5\ Cl$	− 1.5
$C_2H_5\ CHO$*	− 2.7	$C_6H_5\ OH$	− 1.7
$C_2H_5\ CN$	− 3.3	$C_6H_5\ CHO$	− 2.8
$C_2H_5\ NO_2$	− 4.0	$C_6H_5\ CN$	− 3.85
* By analogy with CH_3CHO		$C_6H_5\ NO_2$	− 3.9

The different orientation of the dipoles in these two classes of substituents is deduced from the behaviour of the disubstituted benzenes by a method suggested by J J Thomson[2] *o*-Dichlorobenzene, for instance, has a much greater moment than chlorobenzene, because the two CCl-dipoles in this compound are arranged in such a manner as to reinforce one another *p*-Dichlorobenzene, however, behaves in a uniform electrical field as a non-polar substance, giving $\mu = 0$ In this case the two CCl-dipoles are oriented in opposite directions and their effects cancel out Similarly Cl and NO_2 being both of the electro-



1.55 2.25 1.48 0

negative type, it is found that among the nitro chlorobenzenes the *o*-compound ($\mu = 3.78$)[3] gives a higher moment than the *m*- ($\mu = 3.18$) or *p*-compound ($\mu = 2.36$) Among the methyl aminobenzoates, however, where the two groups are of the opposite type, the moment is least ($\mu = 1.0$) in the *o*-compound, of intermediate value ($\mu = 2.4$) in the *m*- and highest ($\mu = 3.3$) in the *p*-compound in which the dipoles reinforce one another Relationships of the same kind are exhibited among the *cis*- and *trans*-isomerides of the ethylene series

Symmetrical molecules such as carbon bisulphide and carbon tetra-

[1] The majority of these values have been determined by J W Williams, C P Smith and J Højendahl, and are taken from Debye's *Polare Molekeln* (Leipzig, 1929) Some of the figures are possibly subject to minor corrections [2] J J Thomson, *Phil Mag*, 1923, 46, 513
[3] All these values of μ are to be multiplied by 10^{-18}

chloride possess zero moment, but it appears that in compounds of this type in which the substituent groups are of a more complex nature the moment may have a finite value Probably in such cases the molecule assumes an unsymmetrical arrangement because of the forces of attraction or repulsion exerted by neighbouring groups upon one another Thus pentaerythritol, $C(CH_2OH)_4$, and certain of its derivatives containing oxygen[1] have been shown to have comparatively large moments Similar difficulties are encountered in predicting the dipole

$C(CH_2OH)_4$	$C(CH_2OAc)_4$	$C(CH_2Br)_4$
$\mu = 2 \times 10^{-18}$	$2\ 6 \times 10^{-18}$	0

moments of complex molecules and also in explaining certain values of disubstituted benzenes As yet the investigation of this subject is still in its infancy.

Evidence is rapidly accumulating to show that many properties of compounds, *e g* dissociation of acids, velocity of chemical reactions, optical activity, solvent effect, etc, may be correlated with the type and magnitude of the dipoles present in the molecule A few examples of this kind are given in the following table (for optical activity and solvent effect, see pp 90, 92) Here also the observed regularities are occasionally subject to exceptions owing to the operation of disturbing factors, the nature of which is not yet fully understood

X	NH_2	CH_3	H	OMe	I	Br	Cl	OH	CN	NO_2
I	—	2 (?)	2 (?)	4 4	5 9	7 1	7 6	15	19	21
II	Small	0 001	0 002	0 033	0 075	0 138	0 155	0 015	0 37	—
III	—	9 4	1 0	—	0 37	0 41	0 47	—	—	0 04
IV	0 31	1 00	—	—	—	1 53	1 32	—	5 71	—

I Molecular Inductive Capacity of C_2H_5X, see H G Rule and T R Paterson, *J C S*, 1924, 2159

II Dissociation constants of monosubstituted acetic acids

III Velocity of hydrolysis of *p*-substituted benzyl chlorides, Olivier, *Rec trav chim*, 1923, 42, 516, 775.

IV Velocity of opening of phthalide ring by alkalis, Tasman, *Rec trav chim*, 1927, 46, 653

10 Optical Behaviour.

A, MOLECULAR REFRACTION.

The molecular refraction of a substance is the product of the specific refraction into the molecular weight ·

$$\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$$

(where n = index of refraction, M = molecular weight, d = density)

In general it is an additive property, the molecular refraction of a compound being equal to the sum of the atomic refractions of the elements contained in it

[1] A complication is introduced in the case of oxygen compounds owing to the angle subtended by the two oxygen valencies

The following table gives the atomic refractions of some of the elements, in the one column as referred to sodium light (Conrady), and in the other to the red hydrogen line (Bruhl) —

Element	Sodium light	Red hydrogen line	
C	2 500	2 365	Carbon in a single bond
H	1 051	1 103	
O'	1 521	1 506	Hydroxylic oxygen
O"	2 287	2 328	O in the carbonyl group
O<	1 683	1 655	O in simple ethers
Cl	5 998	6 014	
Br	8 927	8 863	
I	14 120	13 808	
=	1 707	1 836	Double bond between two carbon atoms
≡		2 220	Triple carbon linking

The atomic refraction of nitrogen varies considerably according to the compound in which it occurs The extreme values are 2 446 and 4 363 for sodium light, and 2 311 and 4 105 for the red hydrogen line

From the above data it is possible to calculate the molecular refraction of a series of compounds by summation of the atomic refractions, and for the most part the values so obtained are in good agreement with those determined by experiment

As may be seen from the table, the atomic refraction of polyvalent elements, such as carbon or oxygen, varies with the state of combination, and from the experimentally determined molecular refraction it is therefore possible to draw conclusions as to the constitution of a compound Valuable work in this sphere has been carried out by Bruhl and Auwers, who have shown that molecular refraction and dispersion are partly additive and partly structural in character

The molecular refraction of benzene, for example, points to the presence of three double bonds in the ring, corresponding to the formula of Kekulé According to Bruhl[1] the molecular refraction also affords a means of distinguishing between the keto and enol forms of desmotropic compounds, since the double bond of the enol form betrays itself in the characteristic value of the ethylene bond

For information as to **molecular dispersion** see Cohen, *Organic Chemistry*, Part II (Arnold)

B Optical Rotation[2]

The theoretical treatment of optical activity has already been given in connection with stereoisomerism, see p 32 *et seq*

Specific Rotation —An exact quantitative expression of the degree

[1] Brühl, *Z phys. Ch*, 1900, 84, 31 [2] *Cf* Walden, "Ueber das Drehungsvermögen optisch aktiver Korper," *Ber*, 1905, 38, 345, Landolt, *Das optische Drehungsvermögen organischer Substanzen und die praktischen Anwendungen derselben*, 2nd edition, 1898, G Wittig, *Stereochemie* (1929)

of activity of a fluid or dissolved compound was made possible by the introduction of the term *specific rotation* $[\alpha]$

The value of the specific rotation is given by an expression such as

$$[\alpha]^t_\lambda = \frac{\alpha \times 100}{l \times c} \quad \text{or} \quad \frac{\alpha \times 100}{l \times d \times p}$$

in which λ represents the wavelength of light employed, α = angle of rotation observed, t = temperature, l = length in decimetres of solution traversed, c = number of grams of substance contained in 100 c c of the solution, d = density of solution, and p = number of grams substance in 100 grams of solution A clockwise or dextro rotation as seen by an observer using the polarimeter is written as +, and a counter-clockwise or laevo rotation as –

The product of the specific rotation and the molecular weight M is known as the *molecular rotation*, and is represented as follows

$$[M] = \frac{[\alpha] M}{100}$$

In this case the hundredth part of the product is taken, in order to avoid unwieldy numbers

Variation in the Rotation with Experimental Conditions—Owing to the great interest aroused in stereochemical problems a considerable amount of experimental data dealing with optical rotation has gradually been accumulated In most cases (with the exception of aqueous solutions of certain sugars) the specific rotation varies with the concentration of the solution, and frequently also with the nature of the solvent employed Thus, for example, *d*-tartaric acid is dextrorotatory in aqueous solution but laevorotatory when dissolved in a mixture of ether and acetone

In some instances the rotation of a freshly prepared solution of an active substance is found to change progressively with time, until equilibrium is finally attained This is known as *mutarotation* and is well illustrated in the case of glucose (see glucose, p 298) The alteration in activity goes hand in hand with an intramolecular change

Every chemical action undergone by an active compound produces a visible change in the rotation, the magnitude and direction of which is dependent on the constitution of the active molecule, as well as on the chemical character of the reagent employed

The greatest alterations in specific rotation which have so far been effected by chemical action on a given asymmetric carbon atom, occur when certain active hydroxy compounds are treated with inorganic substances to form complexes and halogen derivatives In these cases the degree of asymmetry, and therewith the optical properties, are often fundamentally modified

Example I—The addition of alkali tungstates, molybdates and uranates, and of beryllium, titanium and zirconium compounds to certain optically active substances produces a considerable change in rotation, as illustrated in the following table —

	$[\alpha]_D$		
	Malic Acid	Tartaric Acid	Quinic Acid
In aqueous solution	− 2°	+ 13·2°	− 43·1°
With ammonium molybdate	+ 74·0	+ 780·0	− 66·0
,, alk. uranyl nitrate	− 50·0	+ 265·0	− 102·0

Example II.—It has been shown by Walden[1] that unexpected changes occur during the interconversion of the active malic and chlorosuccinic acids, viz. :—

(*a*) By the action of phosphorus pentachloride laevorotatory malic acid, or its ester, is converted into dextrorotatory chlorosuccinic acid, or its ester.

(*b*) Laevorotatory chlorosuccinic acid is converted by certain reagents (*e.g.* silver oxide) into laevorotatory malic acid, and *d*-chlorosuccinic acid into the corresponding *d*-malic acid. On the other hand, other reagents (potassium or ammonium hydroxide) convert *l*-chlorosuccinic acid into *d*-malic acid, and *d*-chlorosuccinic acid into *l*-malic acid. Further information on this subject is given in a later chapter (see p. 278).

This change in configuration—generally known as the *Walden inversion*—has been further investigated by Emil Fischer.[2] The cycle of changes discovered by Walden between the active malic and halogen substituted succinic acids has been extended by Fischer's discovery of the similar series of changes undergone by the α-amino and the α-halogen acids. The latter investigator also proved that the same substitution reaction may produce different optical results when small changes are made in the groups united to the asymmetric carbon atom.

The explanations of the phenomenon given by Fischer and Werner agree in assuming the formation of an intermediate product in which partial valencies are involved. Hence the Walden inversion may be closely related to the process of substitution.

An explanation based on the electronic theory has recently been advanced by J. Kenyon and H. Phillips, arising out of an investigation of the changes undergone by derivatives of *l*-β-octanol.[3]

Molecular Constitution and Magnitude of Rotatory Power

Many attempts have been made to connect the constitution of an optically active compound with the magnitude of its rotation. Guye, in 1890, suggested that the rotatory power was dependent on the degree of asymmetry of the compound, as calculated from the masses of the four radicals and the distances of their centres of gravity from the asymmetric atom to which they are attached. In the same year Crum Brown advanced the hypothesis that the rotation was a function of the chemical constitution as well as of the mass of each side chain. Whilst Guye's theory proved to be untenable in the light of further research, later investigations have indicated that the same *constitutional* influences which are exhibited in properties such as inductive capacity, dissociation

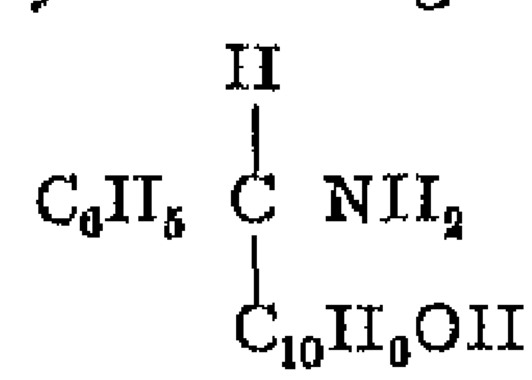
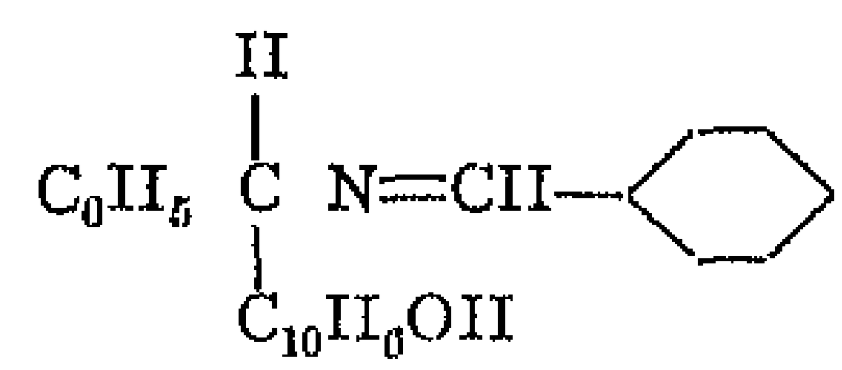
[1] Walden, *Ber.*, 1899, **32**, 1855. [2] Fischer, *Ann.*, 1911, **381**, 123. Werner, *Ann.*, 1911, **386**, 65. See also the comprehensive survey by Walden. *Optische Umkehrungserscheinungen* (Vieweg and Son, Brunswick, 1919). [3] J. Kenyon and H. Phillips, *Trans. Faraday Soc.*, **1930**, 451.

constants and velocity of chemical reaction are also to be observed in optical activity

Cyclic compounds having asymmetric atoms in the ring commonly exhibit higher rotations than those of open-chain type, and the proximity to the asymmetric centre of unsaturated linkings (especially when conjugated) also tends to raise the rotatory power An interesting constitutional regularity was discovered by Frankland and confirmed in numerous cases by Pickard and Kenyon and their co-workers In a homologous series, the smooth curve representing the rotatory powers frequently shows sudden deviations as the growing chain attains a length of 5, 10, 15, etc, atoms This is explained on the basis of Baeyer's Strain Theory, on the supposition that the growing chain assumes a spiral formation in space, so that every increase of 5 or 6 atoms again brings the free end into the neighbourhood of the beginning of the chain Such abnormalities are also found in other properties of homologous compounds (see pp 351, 413, 418)

Influence of Polar Substituents contained in the Active Molecule

One of the earliest researches bearing on this point is that of Betti,[1] who examined the rotatory powers of a number of Schiff's bases (II) prepared by condensing *d*-β-naphthol-benzylamine (I) with

I  II 

benzaldehyde and various substituted benzaldehydes On introducing substituents into the benzaldehyde ring it was found that their influence on the rotatory power of the Schiff's base corresponded approximately to their effect on the dissociation constant of benzoic acid

Similar relationships have been observed among other optically active derivatives by Rule and co-workers The rotatory powers of the

Homogeneous l Menthyl Esters of Monosubstituted Acetic Acids,
$X\ CH_2\ COOC_{10}H_{19}$

X	$\mu \times 10^{18}$	$[M]^{20}_{5461}$	$k \times 10^5$
NEt_2	+1 4	−154 6°	Small
NMe_2	+1 4	156 9	"
H	±0	157 3	1 8
CH_3	±0	160 2	1 4
COOH	−0 7 (?)	160 2	160
OCH_3	−1 2	165	33
OH	−1 7	165 (at 94°)	15
Br	−1 5	169	138
Cl	−1 5	171	155
CN	−3 8	174	370

[1] For a summary see M Betti, *Gazz. chim Ital*, 1923, 58, 424, *Trans Farad Soc*, 1980, 337

l-menthyl esters of mono-substituted acetic acids, for example, were found to increase with the dissociation constants k of the acids[1] An even closer agreement is obtained by comparing the rotatory powers directly with the dipole-moments (μ) characteristic of the substituent groups (see p 84), as may be seen from the preceding table[2]

Polar influences of the same nature have also been traced in the molecular rotations of *l* menthyl ethers,[3] and of the *l* menthyl and β-octyl esters of substituted benzoic acids[4]

Intimately connected with this question is the modification in rotatory power which occurs when an optically active acid or base is converted into a salt

As indicated below, the electrical influence of a polar group upon the hydrocarbon chain to which it is attached may be supposed to depend on the nature of the nearer end of the dipole, and in the case of the carboxyl group is therefore positive in character On the other hand, the corresponding influence of the amino group is negative When the acid or amine is ionised as in the process of salt formation, we may consider that an electrical charge is superimposed which tends to reverse the

$$\mathrm{R}\ \overset{+-}{\mathrm{COOH}} \longrightarrow \mathrm{R}\ \overset{\ominus}{\mathrm{COO}}, \qquad \mathrm{R}\ \overset{-+}{\mathrm{NH_2}} \longrightarrow \mathrm{R}\ \overset{\oplus}{\mathrm{NH_3}}$$

normal polar effect of the ionised group upon the chain[1]

The result of these changes may be observed not only in their effect upon the ionisation of a second carboxyl group present in the molecule, but also in the optical changes undergone by many active acids and bases of simple constitution In the form of their salts these compounds frequently exhibit a greatly diminished rotation or even a reversal of sign Examples of this kind are lactic, methoxysuccinic and valeric acids, and amylamine, nicotine and coniine

CH_3 CHOH COOH	$C_5H_{11}NH_2$
d-Lactic acid, $[M]_D$ + 3 3° (in water, c = 5)	Amylamine, $[M]_D$ − 5 2°
Sodium salt, $[M]_D$ − 10 9° (in water, c = 5)	Hydrochloride, $[M]_D$ + 11 7° (in alcohol)

In more complex compounds, the direction of the changes in rotation may be affected by the constitution of the rest of the molecule But even in such cases it is often observed that the introduction of an electropositive group (NH_2 or NMe_2) modifies the rotatory power in the opposite sense to an electronegative group (COOH) and that on ionisation the characteristic influence is reversed This is illustrated by

[1] H G Rule and J Smith, *J C S*, 1925, 127, 2188 [2] H G Rule, R H. Thompson and A Robertson, *J C S*, 1930, 1887 [3] H G Rule and H. Tod, *J C S*, 1931, 1929
[4] H G Rule, *Trans Farad. Soc*, 1930, 321

the following rotatory powers, $[M]_{5461}$ (in alcohol, $c = 5$), relating to *l*-menthyl benzoate and its ortho-carboxy and ortho-amino derivatives [1]

$C_6H_5 \cdot COOC_{10}H_{19}$	$o\text{-}C_6H_4\begin{smallmatrix} COOC_{10}H_{19} \\ COOH \end{smallmatrix}$	$o\text{-}C_6H_4\begin{smallmatrix} COOC_{10}H_{19} \\ NMe_2 \end{smallmatrix}$
− 275°	Acid − 346° Sod salt − 260°	Amine − 250° Hydrochloride − 292°

On the other hand, sulphonic acids are already strongly ionised in aqueous solution and undergo relatively little change in rotation on being converted into their salts

From these investigations Rule has concluded that the rotation of an active compound is mainly dependent in sign and magnitude upon the nature and arrangement of the dipoles in the molecule

Solvent Influence

In general, the rotatory power of a dissolved substance varies with the nature of the solvent, the variations being in some cases of surprising magnitude The task of establishing a connection between the rotatory power of the dissolved substance and the constitution of the solvent molecule has proved a difficult one, but definite progress is at last being made by studying the problem from the polar standpoint

In 1926, Rule and Mitchell [2] found that the molecular rotations of various aliphatic octyl esters were depressed by solution in solvents derived from benzene, the extent of the change being dependent upon the polarity of the medium This indication that the rotatory power may be related to the polarity of the solvent has recently been confirmed in a striking manner by Rule and McLean [3] in an investigation of *l*-menthyl methyl naphthalate A few of their observed rotations are reproduced in the following table

Rotatory Powers of l-Menthyl Methyl Naphthalate in Solvents

Solvent	$[M]_{5461}$	$\mu \times 10^{18}$	Solvent	$[M]_{5461}$	$\mu \times 10^{18}$
$CH_3 \cdot NO_2$	− 219°	3 78	$C_6H_5 \cdot CN$	372°	3 85
CH_3CN	239	3 05	$C_6H_5 \cdot NO_2$	423	3 89
CH_3CHO	316	2 71	C_6H_5CHO	432	2 75
CH_3I	336	1 66	$o\text{-}C_6H_4Cl_2$	433	2 24
$CH_3 \cdot OH$	383	1 64	$C_6H_5NH_2$	413	1 60
$CH_3 \cdot COOH$	423	0 75 (?)	$C_6H_5 \cdot Cl$	463	1 52
CS_2	437	0	$C_6H_5 \cdot Br$	466	1 50
CCl_4	563	0	$C_6H_5 \cdot I$	465	1 25
$C(NO_2)_4$	651	0	$C_6H_5 \cdot OCH_3$	466	1 25
Hexane	653	0	C_6H_6	513	0
Cyclohexane	688	0	$C_6H_5 \cdot CH_3$	516	0

Here also the highest rotations are given in non-polar media and the variations in rotatory power appear to be governed chiefly by the

[1] H G Rule and MacGillivray, *J C S*, 1929, 401 [2] H G Rule and R K S Mitchell, *J C S*, 1926, 3202 [3] H G Rule and A. McLean, *J C S*, 1931, 669 Compare also Rule and J Hill, *J C S*, 1931, 2652

dipole moment of the solvent The full effect of the more polar liquids, however, is not brought into play, because the dipoles in such compounds are usually considerably masked by *dipole-association*[1] (see fig 19), which results in a greatly reduced external field

It is probable that the changes in rotation are mainly due to dipole association between solute and solvent, although in certain cases definite union may be involved

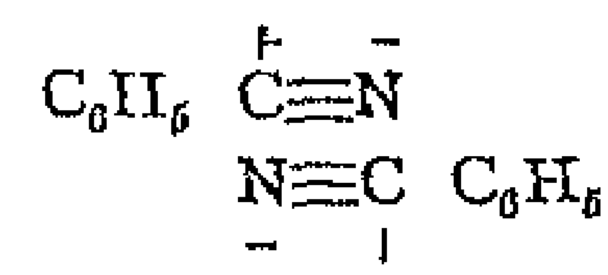


FIG 19

As we have seen in the previous section the magnitude of the rotatory power of a given compound is related to the magnitude and arrangement of the dipoles in the active molecule If, therefore, the electrical field of these dipoles is diminished through dipole association, either between solvent and solute or between the optically active molecules themselves, their characteristic influence on the rotation must also be lowered In the case of the octyl and menthyl esters discussed above the introduction of an electronegative substituent increases the rotatory power, dipole association with other polar molecules will therefore tend to lower it Similar relationships are observed in a number of compounds, although in many cases no regularities have yet been traced

The rotatory power of *l*-menthyl methyl naphthalate in solution forms one of the most complete examples of polar solvent effect yet discovered, the fundamental significance of which is not limited to the sphere of optical activity We have here a method of investigating the interplay of molecular forces which may eventually give valuable information concerning the more general problem of solvent influence

C MAGNETIC ROTATION

In the year 1845 Faraday discovered the property possessed by transparent optically inactive substances of rotating the plane of polarised light when they were placed in a magnetic field More recently, W H Perkin, sen,[2] has made a careful study of the relation between the constitution of carbon compounds and the magnitude of this rotation

The liquid under investigation, contained in a polarimeter tube, is placed axially between the poles of an electromagnet, on excitation of the magnetic field a rotation of the plane of polarisation to the right or left may be observed, corresponding to the polarity of the magnets or the direction of the current The rotation lasts only so long as the magnetic field is maintained, and in this way differs from the rotation produced by optically active compounds

For a given temperature (15°), length of tube (10 cm) and the employment of the same source of illumination (usually sodium light), the *magnetic rotation* of a substance is given by the general expression $\frac{\alpha M}{d}$, where α is the angle of rotation, M the molecular weight and d the density Perkin used water as

[1] See Rule and McLean, *loc cit* [2] *J C S*, 1884 1907

the standard of comparison, and termed the ratio of the rotation $\frac{\alpha M}{d}$ of the substance to that of water $\frac{\alpha' M'}{d'}$ the *molecular magnetic rotation*, where α and α' have been determined at the same current strength.

It was found that the magnetic rotation of a homologous series could be represented by the general expression $(a+nb)$, in which a is a constant having a special value for each homologous series, n is the number of CH_2 groups and b is the difference in rotation corresponding to a difference of CH_2, the magnitude of which approximates to 1·023 units. The formula holds only for compounds containing at least one CH_2 group in the molecule. As in the case of molecular refraction (p. 86), the constitution exerts a definite influence on the magnetic rotation. A double bond, for example, increases the constant a considerably, although in a degree varying with the class of compound.

11. Heat of Formation and Heat of Combustion

The heat of combustion of a substance is that quantity of heat which is developed during its complete combustion, and is usually quoted as the number of calories (large) per gram of substance.[1] It is of interest from the practical as well as the theoretical point of view. From it may be calculated the heat of formation and other thermochemical data, and on comparing the heats of combustion of different substances, certain constitutional regularities are observed. The calorific value of substances rich in carbon (such as coals) depends in the main on the heat of combustion.

Similarly the heat of combustion is of importance in connection with food stuffs, since these represent energy which is utilised by slow combustion in the body itself.

A special method has been devised by Berthelot for determining the heat of combustion, details of which may be found in text-books of practical physical chemistry.

Certain relationships have been established between the constitution of organic compounds and the heat of combustion. For example, an almost constant difference of 158 calories is found for each difference of CH_2 in the homologous hydrocarbons, and similar regularities may be traced in other homologous series. Among the higher members of the benzene hydrocarbons, each additional CH_2 results in an increment of approximately 155 calories to the heat of combustion.

In the aliphatic hydrocarbons the presence of a double bond raises the heat of combustion by 15·5, and a triple bond by 43·9 calories.[2] Consideration of the heat of combustion of aromatic compounds, on

[1] A large calorie is the amount of heat required to warm 1 kg. of water from 15° to 16°.
[2] For further relations between the constitution and the heat of combustion of unsaturated compounds, see Auwers, Roth, and Eisenlohr, *Ann.*, 1910, 378, 239, 249, 267; *Ber.*, 43, 1063.

the other hand, leads to contradictory conclusions regarding their constitution[1]

As an example of the application of thermochemical measurements to constitutional problems, the work of Stohmann on the heat of combustion of camphoric acid may be quoted From the experimental data he concluded that this substance was not a derivative of tetramethylene, but either a penta- or a hexamethylene carboxylic acid Recent investigations have since proved camphoric acid to be derived from pentamethylene

In general, isomeric compounds develop equal heats of combustion when they are of similar chemical character, *e g*, methyl acetate and ethyl formate On the other hand, if they are chemically different, their heats of combustion also differ, thus the value for methyl formate, HCOO CH_3, which has carbon atoms linked through oxygen, is greater than that of the isomeric acetic acid, H_3C COOH, similarly the figure for dimethyl ether is greater than that for the isomeric ethyl alcohol

In the case of geometrical isomers, it would appear, so far as we are able to judge from the available experimental data, that the form possessing the higher melting-point, usually the *trans*-form, has the lower heat of combustion An examination of various stereoisomeric aromatic acids has shown a complete parallel between heat of combustion and dissociation constant Whether the isomerism is due to the presence of single or multiple bonds or to spatial configuration, it is found, with few exceptions, that the more stable form has a smaller heat of combustion and a smaller dissociation constant than the labile isomeride[2]

The **heat of formation** of a substance is the amount of heat liberated in the formation of the substance from its elements This value may be positive or negative It is positive in those compounds termed *exothermic*, which are formed with evolution of heat, and negative in *endothermic* compounds produced with absorption of heat An example of the latter class is acetylene The numerical value for endothermic compounds is consequently written with a negative sign The heat of formation of organic compounds is determined indirectly, by subtracting the heat of combustion of the compound from the sum of the values for the individual elements

For example, the heat of combustion of 1 gm. mol of methane (16 gms CH_4) is 210 8 cal, whereas that of the individual elements (12 gms C +4 gms H) gives a total of 232 cal, the heat of formation of methane therefore is 232 − 210 8 = 21·2 cal[3]

NOMENCLATURE OF ORGANIC COMPOUNDS

In organic chemistry one and the same compound is frequently described with equal accuracy in a number of ways, an author

[1] *Cf* Stohmann, *J pr Ch*, 1893 [2], 48, 453 Brühl, *Ber*, 1894, 27, 1065 Roth and Oestling, *Ber*, 1913, 46, 309 [2] Roth and Stoermer, *Ber*, 1913, 46, 260 [3] For the relationship between constitution and heat of formation of organic compounds, see Brühl, *J pr Ch*, 85, 181, 209.

employing different names as he desires to lay emphasis on the properties of the compound or on its relationship to some other substance For the latter reason many animal and vegetable products have been named in reference to their origin, *e.g.*, urea, uric acid, malic acid (from apples) and citric acid Owing to the rapid development of this branch of science the need for a standard system of nomenclature was realised at an early stage The position of things in 1892 was such that an international commission was called to meet in Geneva, for the purpose of deciding upon a system of nomenclature by which the constitution of an organic compound could be simply and clearly expressed This task was only partly completed, but the findings of the Geneva commission are frequently used, more particularly in describing compounds of the fatty series

In general, organic compounds may be referred back to one or another of a limited number of parent or index substances (*cf* p 20), from which they may be considered to be derived by replacement of hydrogen with other atoms or groups The Geneva nomenclature is built up from the names of these parent compounds by the addition of certain syllables, such as *-ol* for alcohol, *-al* for aldehyde, *-on* for ketone and *-saure* for carboxylic acid (in English the last two become *-one* and *-acid* respectively) Unsaturated compounds take the suffix *-en* (*-ene*) for a double bond, and *-in* (*-ine*) for a triple bond Thus ethanal is acetaldehyde, and propenol is allyl alcohol Most of the other substituent groups are indicated in the usual manner by prefixes In the case of compounds possessing several characteristic groups, these are named in a certain agreed sequence, and two or more of the same groups, if present in a compound, are indicated by the prefixes di-, tri- and so on The respective positions of the substituents are shown by lettering or numbering Unfortunately the proposals put forward have not proved suitable for adoption *en masse*, with the result that different countries, and even different scientific publications in the same country, often show considerable variations in nomenclature, as may readily be seen by tracing the abstracts of papers dealing with complex organic compounds through the British, American and Continental journals.[1] Consequently it is not possible to give here more than a brief outline of the modifications of the Geneva nomenclature at present in use. Further details will be given as each new class of compounds comes under discussion

It will readily be understood that the Geneva practice of referring back to the simplest parent substance leads to considerable difficulty when applied to substances possessing several characteristic functions For example, the compound $CHO.CH_2$ $CHOH$ CO $COOH$ would be

[1] In *An Introduction to the Literature of Chemistry* (F A Mason, Clarendon Press, 1925) will be found a list of the more important chemical journals, reference books, etc, with hints as to their use

termed (omitting numbering) pentanolalone-acid. In modern practice therefore it has been found necessary to modify these principles and simplify matters by the use of larger index compounds, wherever these are already well known under a short name.

As may be seen from the journals of the Chemical Society and the American Chemical Society, the tendency is to employ the largest index compound available and to express the chief function of the substance in the ending.[1] Substituent radicals according to American practice are mentioned in alphabetical order, and in English after the sequence laid down by the Chemical Society. The Chemical Society uses Greek letters for all open chain compounds, the lettering commencing with the end C-atom except in the case of carboxylic acids and nitriles, when a beginning is made with the atom adjacent to the characteristic group. Isomeric open chain compounds are represented as substitution derivatives of the longest carbon chain in the formula. Ethylene homologues take the ending *-ene*, and those of acetylene *-ine*, wherever possible. The ending *-ol*, is reserved exclusively for alcoholic or phenolic compounds, all others taking *-ole*, *e.g.*, indole, anisole. Similarly, basic substances are indicated by names ending in *-ine*, the termination *-in* being restricted to certain neutral compounds, viz., glycerides, glucosides, bitter principles and proteins (*e.g.*, palmitin, amygdalin, albumin). In Beilstein's *Lexicon* the term *oxo-* is used to describe the keto group.

Ring compounds are named in accordance with the system laid down in Richter's *Lexicon der Kohlenstoff-verbindungen*, the position of substituents being indicated by numbers. In naming substituted derivatives of compounds such as phenol, aniline or benzoic acid, the characteristic radical of the parent substance is assumed to occupy position 1.

For the designation of commonly occurring groups, Vorländer has made the following suggestions. Monovalent organic radicals, whether of fatty or aromatic nature, are termed *alkyl* groups. A further distinction may be made by calling fatty groups *alphyl*, aromatic groups *aryl*, and groups of mixed fatty and aromatic character *alpharyl*. Furthermore, groups of acidic nature may be described as *alphacyl* and *aracyl* respectively.

[1] For an interesting discussion on nomenclature and indexing, see A. M. Patterson and C. E. Curran, *J. Am. C. S.*, 1917, 39, 1623.

PART I

The Aliphatic or Fatty Compounds

THE numerous compounds classified under this title may be regarded as derived from the hydrocarbon methane, CH_4, and are therefore termed methane derivatives. Since the common animal and vegetable fats similarly fall under this heading, the whole series is frequently known as the aliphatic or fatty series. Structurally, compounds of this type are distinguished by containing open carbon chains in contrast to the closed chains or rings of the aromatic or benzene series.

Organic research, which for fifty years had been pursued for the most part among aromatic compounds, has recently turned towards the investigation of aliphatic derivatives. New sources have been discovered for the preparation of aliphatic substances, and the growing interest in physiological chemistry is giving rise to more and more work in this branch, since the chief reactions of plant and animal life are of an aliphatic nature. The reduction processes of plant synthesis, and the oxidation changes which occur in plant and animal cells, lead alike to the formation of methane derivatives.

I

Hydrocarbons

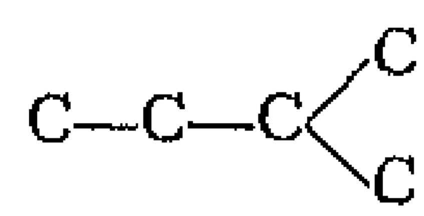
I.—SATURATED HYDROCARBONS OR PARAFFINS, C_nH_{2n+2}

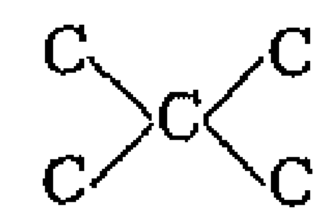
Nomenclature.—The homologous series of hydrocarbons possessing the general formula C_nH_{2n+2} is termed "saturated," in contradistinction to the ethylene series which exhibits pronounced additive or unsaturated properties. Not only are these compounds incapable of uniting directly with hydrogen, for example, but they are also extraordinarily resistant to attack by the majority of reagents, such as strong bases and acids, a peculiarity which has led to them being known as the paraffin series (*parum affinis*, little affinity). The names of the individual members are derived from the Greek numerals indicating the number of carbon atoms in the molecule, by the addition of the syllable -ane, *e.g.*,

hexane, C_6H_{14}, heptane, C_7H_{16}, octane, C_8H_{18}, and so on Only the first four members have special names, viz, methane, CH_4, ethane, C_2H_6, propane, C_3H_8, butane, C_4H_{10}

As already mentioned, the fourth member of the series exists in two forms, butane and isobutane, and these (p 99) may give rise to different pentanes according as the carbon chain is straight as in I, or branched as in II and III[1]

I C—C—C—C—C

II 

III 

When a carbon atom is combined in such a manner that only one of its four valencies is satisfied by carbon, it is termed a primary carbon atom, similarly if two, three or all four valencies are linked to carbon, the atom under consideration is termed secondary, tertiary or quaternary respectively

Those hydrocarbons with straight carbon chains are known as *normal* hydrocarbons in distinction to the *iso*-hydrocarbons containing branched chains

Since other compounds of the fatty series may be derived from the paraffins by replacement of one or more hydrogen atoms by other elements or groups, it has in some cases been found convenient to coin special names for the hydrocarbon residues or radicals which remain after removal of such hydrogen atoms

Monovalent radicals, of the general formula C_nH_{2n+1}, which result from the paraffins by the removal of one hydrogen atom, are known under the general name of *alkyl* (or alphyl) groups (p 97) The name of each individual group is obtained from that of the corresponding saturated hydrocarbon by changing the end syllable -ane into -yl, *eg*, *methyl*, CH_3—, *ethyl*, C_2H_5—, *propyl*, C_3H_7— For reasons which will be seen later (p 142) the group C_5H_{11}, instead of being called pentyl, is known as the *amyl* group

Ethyl and **methyl** have now been shown to exist in the free state, but even at low temperatures they polymerise rapidly. In the former case the product has been identified as butane[2]

The **divalent radicals** resulting from the saturated hydrocarbons by removal of two atoms of hydrogen, have the general formula C_nH_{2n}, and are named after the parent hydrocarbon by changing the end syllable -ane into -ylene, *eg*, *methylene*, CH_2=, *ethylene*, C_2H_4=, *propylene*, C_3H_6=

Similarly, the **trivalent radicals** of the general formula C_nH_{2n-1} are written with the termination -ine, *methine*, $CH\equiv$, *ethine*, $C_2H_3\equiv$, *propine*, $C_3H_5\equiv$

[1] The number of isomerides rises with surprising rapidity as the number of carbon atoms in the chain increases There are five hexanes, nine heptanes and eighteen octanes theoretically possible [2] Paneth and Lautsch, *Ber*, 1931, 64, 2702, 2709

According to the Geneva proposals the names of the more complex saturated hydrocarbons are derived in the following manner The names given above are retained for those hydrocarbons of normal straight chain constitution The iso-hydrocarbons, containing branched chains, are regarded as alkyl substitution products of the longest straight chain hydrocarbon which it is possible to assume from the formula In dealing with the higher members, the carbon atoms of the longest chain are numbered from one end, by which means the position of the substituting alkyl groups may be indicated The numbering starts at that end of the carbon chain which is nearest the substituting groups In the case where two side chains are attached to a pair of carbon atoms symmetrically situated in the main chain, the numbering commences at the end nearer the simpler side chain In this way we obtain the following, modified to English and American practice (see also p 97)

$$\overset{1}{C}H_3\ \overset{2}{C}H\ \overset{3}{C}H_2\ \overset{4}{C}H_3 \qquad \overset{1}{C}H_3\ \overset{2}{C}H_2\ \overset{3}{C}H\ \overset{4}{C}H\ \overset{5}{C}H_2\ \overset{6}{C}H_3$$
$$CH_3 \qquad\qquad\qquad CH_3\ CH_2\ CH_3$$

2 Methylbutane or β Methylbutane — 3 Methyl 4 ethylhexane or γ Methyl δ ethylhexane

When necessary the carbon atoms of a longer side chain are distinguished by two numbers, the first in normal type indicating the particular atom of the main chain to which the side chain is attached, and a small index number representing the position of the atoms in the latter Those alkyl groups substituted in the side chain are then distinguished as metho , etho , etc , instead of methyl, ethyl, etc

$$\overset{1}{C}H_3\ \overset{2}{C}H\ \overset{3}{C}H_2\ \overset{4}{C}H\ \overset{5}{C}H_2\ \overset{6}{C}H_2\ \overset{7}{C}H_3$$
$$CH_3 \qquad {}^{4^1}CH{-}CH_3$$
$$|$$
$${}^{4^2}CH_3$$

2 Methyl-4[1] metho 4 ethyl heptane

Occurrence and General Properties—The homologous series of the paraffins has been investigated with few omissions from the first member methane, CH_4, to the thirty-fifth member, pentatriacontane, $C_{35}H_{72}$ After the latter, the highest known member[1] is tetrahexacontane, $C_{64}H_{130}$ The first four members of the series are gases under normal conditions, then follow liquids, and from $C_{16}H_{34}$ upwards they are solids at the ordinary temperature As already mentioned, these compounds are very stable towards chemical reagents, even resisting the action of concentrated sulphuric or fuming nitric acid[2] On the other hand, chlorine and bromine interact with comparative ease to form substitution products, from which other derivatives are readily obtainable. The boiling-points of the paraffins rise with increase of molecular weight, among the lower members a difference of CH_2 corresponds to an increase of about 30°, the amount becoming smaller as the series is ascended

Immense quantities of saturated hydrocarbons are found free in nature as *petroleum*, or *mineral oil*, the American variety of which consists almost exclusively of paraffins, and is a mixture of many members of the series from the lowest to the highest *Ozokerite* or

[1] Gascard, *Ann. Chim* , 1921, 15 (ix), 332 [2] For the reaction of nitric and nitro sulphuric acids on the paraffins, see Markownikoff, *Ber* , 1899, 32, 1441 , Nametkin, *Ber* , 1909, 42, 1372

earth-wax, found in Galicia, is a mixture of the solid members, and products rich in paraffins are also obtained on the industrial scale by the distillation of fats and brown coal

Up to the present the dry distillation of coal has been carried out in such a way that the aliphatic decomposition products first formed are, for the most part, converted into compounds of an aromatic nature (coal tar) by subsequent contact with the glowing walls of the retort It has been shown, however, by the work of Bornstein, Pictet, Wheeler and Franz Fischer, that in the distillation of coal by the *low temperature carbonisation process*, or under reduced pressure, the primary distillate is composed mainly of aliphatic compounds By employing such a process on the large scale it is now possible to obtain from coal all the products characteristic of the petroleum industry (see also pp 106, 368)

Methane, *marsh gas*, CH_4 *Occurrence*—From many places in the earth's surface an issue of "natural gas" occurs, which consists of methane and other homologues of the paraffin series, together with a little admixed carbon dioxide and nitrogen At Baku, for example, the burning gas constitutes the "holy fires of Baku," and attracted the attention of the fire-worshippers as early as 600 A D In America, natural gas has been harnessed for lighting and the production of power It also issues from the seams in coal-mines, where by diffusing into the atmospheric air it forms an explosive mixture (fire-damp) Methane is produced in considerable quantities, and in a comparatively pure state, by the putrefaction of organic matter and the fermentation of cellulose under stagnant water, hence the name of marsh gas For similar reasons (reductive fermentation of cellulose and decomposition of proteins) it is present in the intestinal gases, more especially of herbivorous animals. In addition, it forms one of the chief components of coal gas

Preparation—Methane is obtained by the following methods:—

1 In the laboratory it may be conveniently prepared by heating a mixture of sodium acetate and soda-lime The active constituent of soda-lime in this reaction is sodium hydroxide, but the pure alkali is not used owing to its corrosive influence on the glass of the containing vessel

$$H_3C\ COONa + NaOH = CH_4 + Na_2CO_3$$

2 Another laboratory method is to boil aluminium carbide with water [1]

$$C_3Al_4 + 12H_2O = 3CH_4 + 4Al(OH)_3$$

3 By the reduction of methyl iodide with nascent hydrogen, *e g*, by means of alcohol and the aluminium-mercury couple, or zinc and hydrochloric acid

$$CH_3I + 2H = CH_4 + HI$$

[1] Moissan, *C r*, 119, 16 Methane prepared in this way is always contaminated with hydrogen (20 per cent) and other impurities

The following methods are of importance from the theoretical rather than the practical standpoint

4 Methane is produced together with ethylene and acetylene by the combination of carbon and hydrogen in the electric arc,[1] $C+4H=CH_4$ This reaction deserves mention since it provides a method of synthesising methane from its elements

By the *complete synthesis* of an organic compound is meant the formation of the compound from its constituent elements, or from such simpler compounds as have already been synthesised from their elements

5 Another synthesis of methane was effected by Berthelot, by passing a mixture of hydrogen sulphide and carbon bisulphide vapour over heated copper Carbon bisulphide and hydrogen sulphide may both be obtained from their elements, so that the synthesis may be expressed by the following equations —

$$C+2S = CS_2, \quad H_2+S = H_2S, \quad CS_2+2H_2S+8Cu = CH_4+4Cu_2S$$

6 Carbon monoxide and carbon dioxide, on being mixed with hydrogen and led over reduced nickel at 250° to 300°, are both reduced to methane [2]

$$CO+6H = CH_4+H_2O, \quad CO_2+8H = CH_4+2H_2O$$

7 Methane is also formed by the decomposition of zinc methyl, $Zn(CH_3)_2$, or more conveniently of methyl magnesium iodide, with water [3] Methyl magnesium iodide also interacts with ammonium chloride to give methane,

$$Zn(CH_3)_2+2H_2O = Zn(OH)_2+2CH_4$$

$$CH_3\,MgI+H_2O = CH_4+Mg\begin{matrix}\diagup I\\ \diagdown OH\end{matrix}$$

$$2CH_3\,MgI+NH_4Cl = 2CH_4+NH_2MgI+MgICl$$

Methods 1, 3 *and* 7 *may be applied in a similar manner to the preparation of higher homologues of the paraffin series*, the best general method perhaps being the decomposition of alkyl magnesium halides with ammonium chloride, which yields the hydrocarbons directly in the pure state

In addition, the following special methods are available —

8 Synthesis from lower members, for example, in order to prepare ethane from methane, a hydrogen atom of the latter may be replaced by halogen and the methyl halide so obtained treated with metallic sodium (Wurtz reaction), zinc (Frankland) or silver,

$$2CH_3I+2Na = C_2H_6+2NaI$$

9 Addition of hydrogen to unsaturated hydrocarbons (see ethane)

[1] Bone and Jerdan, *J C S*, 1901, 79, 1042 [2] Sabatier and Senderens, *C r*, 134, 514, 689 [3] Grignard, *Ann chim phys*, 1901, 24, 438 Spencer, *Ber*, 1908, 41, 2302 Clarke, *J Am C S*, 1908, 30, 1144

10 Reduction of alcohols, ketones and carboxylic acids

11 Electrolytic reduction of acetoacetic ester[1]

12 Distillation of coal, lignite or wood, at comparatively low temperatures (see pp 101 and 106)

Properties of Methane—Methane is a colourless and odourless gas, liquefiable at 11° under a pressure of 180 atmospheres, and boiling at −164° At still lower temperatures it solidifies to a crystalline mass of melting-point −186° The gas is soluble to some extent in cold water, one litre of water at +4° dissolving 49 cubic centimetres Methane is combustible, burning with a slightly luminous flame to form carbon dioxide and water ($CH_4+2O_2=CO_2+2H_2O$) When mixed with air or oxygen and ignited, methane explodes violently, dangerous mixtures of this type occur in coal-mines as fire-damp Chlorine has no action on methane in the dark, but in diffused daylight chlorine-substituted derivatives[2] are formed, *e g* —

$$CH_4 + 2Cl = HCl + CH_3Cl, \text{ Methyl chloride}$$

As will be seen later, these substitution products may be utilised for the conversion of methane into other compounds

The presence of *methane may be detected* by treatment with ozonised oxygen, when it is converted into formaldehyde Even small amounts of the latter are readily identified, owing to its characteristic reactions

$$CH_4 + 2O_3 = CH_2O + H_2O + 2O_2$$

Ethane, $H_3C\cdot CH_3$, is found dissolved in petroleum, and escapes from the earth's surface in many places (*e g*, North America)

It may be prepared by the general methods given above From a theoretical point of view, the discovery of Kolbe[3] in 1848, that ethane was formed by electrolysis of a concentrated solution of potassium acetate, is of great importance The acetanions liberated at the anode interact with one another under the conditions of experiment to give ethane and carbon dioxide At the cathode the discharged potassium ions react with water to form hydrogen and potassium hydroxide

$$\begin{matrix} H_3C—CO_2K \\ H_3C—CO_2K \end{matrix} + 2H_2O = \begin{matrix} H_3C \\ | \\ H_3C \end{matrix} + 2CO_2 + 2KOH + H_2$$

This is the first and most typical of those synthetic reactions which organic chemistry owes to electrolysis Wurtz carried the process a step further by electrolysing a mixture of the salts of two fatty acids, and so by the combination of two different electrolytic residues synthesised higher hydrocarbons

A technical preparation of ethane is based on the combination of ethylene and hydrogen in the presence of finely divided nickel, at high temperature and pressure[4]

[1] Tafel and Jürgens *Ber*, 1909 42, 2548 [2] J Pfeifer, Mauthner and Reithinger, *J pr Ch*, 1919 [2], 99, 239 [3] Kolbe, *Ann*, 1848, 69, 279 [4] C Sprent, *J S C I*, 1913, 32, 171

Ethane is a colourless, odourless gas, which burns in air with a feebly luminous flame; its critical temperature is $+34°$ and critical pressure 50 atmospheres. It is very little soluble in water but more so in alcohol. Chlorine and bromine readily react with it to give substitution products.

Mineral Oil, Petroleum

Occurrence and Formation.—Petroleum is found in many places, of which the most important, from an industrial point of view, are Oklahoma and Pennsylvania in North America, the region in Caucasia having Baku as its centre, and Persia. In addition, it occurs on a considerably smaller scale in Galicia, Roumania, Hungary and numerous other parts.

With regard to the occurrence of these immense deposits, the opinion was long ago advanced by Mendeléeff that they were formed by the action of water on the metallic carbides present in the hot interior of the earth, a view supported later by the work of Moissan, and of Sabatier and Senderens. The discovery, however, that the distillation under pressure of fats, such as fish oil, resulted in the formation of a product strongly resembling American petroleum, led Engler to put forward the hypothesis that petroleum originated from the remains of marine organisms, the nitrogenous content of which decomposed relatively quickly after death of the organism, leaving behind a fatty material which was slowly transformed into petroleum under the influence of pressure and heat, or perhaps of pressure alone.[1] The bulk of the evidence appears to support this theory, and the inorganic hypothesis of the production of petroleum must therefore be abandoned, at all events as regards the larger deposits.

Composition.—Petroleum consists of a mixture of hydrocarbons whose composition varies with the place of origin, and which may contain members of the paraffin series together with cycloparaffins and hydrocarbons of aromatic nature. To isolate from this mixture a constituent of homogeneous composition is a task of considerable difficulty, and rarely attempted in industry.

The *Pennsylvanian oil* is a dark green liquid which appears reddish brown by transmitted light. It contains about twenty different hydrocarbons, and according to the researches of Markownikoff there are, in addition to the normal members, isoparaffins of the general formulæ $R_2CH{\cdot}CHR_2$, CHR_3, and CR_4. The lower paraffins are contained in such proportion that inflammable vapours are given off even at low temperatures. There are also present small amounts of hydrocarbons of the benzene series (cumene and mesitylene) and their reduction products, as well as traces of organic acids and sulphur compounds. Occasionally sulphur compounds are found in larger proportion. On the other hand, the *Caucasian oil* contains about 90 per cent of higher boiling cyclic hydrocarbons of the aromatic series, together with hexamethylene and pentamethylene (naphthenes).

[1] Engler, *Ber.*, 1900, 33, 7; *Z. ang. Ch.*, 1908, 21, 1585; *Ber.*, 1910, 43, 388, 397, 105. Zelinsky, *Ber.*, 1927, 60, 1793; 1929, 62, 1264.

Refining of Petroleum.—The liquid is warmed to expel dissolved gases such as methane, and then distilled, the following three fractions being collected:—

(a) *Naphtha* or *benzine*, boiling-point 40° to 150° (pentanes to nonanes in American oil).

(b) *Illuminating oil* or *kerosene*, boiling-point 150° to 300° (chiefly decanes to hexadecanes in American oil).

(c) The *heavy oil* boiling above 300°, which partly solidifies on cooling. Tar and pitch remain behind in the still.

The crude illuminating oil is purified further by the addition of a little strong sulphuric acid and agitation with compressed air. After removing the layer of sulphuric acid and tarry products, the process is repeated with aqueous sodium hydroxide and again with water; the oil is then redistilled. When the removal of sulphur is necessary this is effected by heating with metallic oxides, such as copper and iron oxide, which are thereby converted into sulphides. The product so obtained is generally known as *petroleum* and is suitable for lighting and heating.

Many risks are attached to the use of insufficiently purified oil for lighting purposes, particularly if lower boiling constituents (naphtha) are present. In order to decide whether an oil is suitable for burning in lamps it is usual to determine its flash point, by warming the oil in a special apparatus and finding by experiment the temperature at which the vapour above the liquid is inflammable. The lowest flash point permissible in Great Britain is 73° F.

It is to be noted that only one fraction of the oil is used for lighting, the others being utilised in a variety of ways.

Naphtha is generally rectified again to yield several volatile fractions, which are collected as follows:—

> *Petroleum ether* or *gasoline*, distilling about 50° to 60°, consists chiefly of pentane and hexane; it may be used for illumination in specially constructed lamps.
>
> *Benzine*, distilling about 70° to 90°, contains a large proportion of hexane and heptane, and should not be confused with benzene from coal tar. It is used for the dry cleaning of all kinds of material.
>
> *Ligroin*, distilling about 90° to 120°, like the foregoing fractions, is extensively used as a solvent for fats, oils and resins.

The heavy oil which distils above 300°, partially decomposing in the process, is also of commercial value. From it is prepared *lubricating oil* for machinery. Unlike the fatty oils, which decompose in the course of time and then attack the metal, these petroleum oils are stable in air and therefore preferable as lubricants. Many of them are even more valuable than the illuminating oils. Another product obtained from heavy oil is *vaseline*, or *petroleum jelly*.

It has already been mentioned that by varying the conditions under which the dry distillation of coal is conducted we may obtain

tars of different compositions The typical constituents produced by the low temperature process (350° to 500° C) are naphthenes and highly viscous oils[1] Under these conditions benzene is either absent or present in traces only, its place being taken by benzine (petroleum ether, etc) Since large yields of tar may be obtained by this process on the technical scale, it should eventually be possible to prepare petroleum hydrocarbons in quantity from coal As yet it is only remunerative where the cheap and readily accessible brown coal is used

Direct Synthesis of Petroleum Hydrocarbons[2]—It has long been known from the experiments of Sabatier and Senderens on the catalytic reduction of carbon monoxide under ordinary pressure, that the final product of reaction is methane Fischer and Tropsch found that the use of a catalyst containing metallic iron and zinc oxide led under ordinary pressures to the formation of a mixture of methane and its higher homologues in place of pure methane A series of catalysts were subsequently discovered which were even more active than the above iron zinc oxide mixture For example, carbon monoxide passed over cobalt mixed with chromium oxide at a temperature of 270° yields not only gaseous homologues of methane, but fluid and solid members of the paraffins, *i e* benzine and other valuable products of the type of petroleum Reference may also be made to the use of catalysts under high pressures, by which means carbon monoxide may be converted into methyl alcohol (see p 135) and its higher homologues (*Synthol*)

In another process invented by Bergius, no catalyst is employed, but coal or the higher boiling fraction of coal tar is heated under pressure with hydrogen This method gives about 5 per cent of lubricating oil, and up to 50 per cent of benzine and Diesel motor oils,[3] and appears to be of considerable industrial value

Paraffin Wax, Ceresine

A product of composition similar to that of the naturally occurring petroleum may also be obtained artificially by the dry distillation of peat, lignite, boghead, cannel coal or bituminous shale

In the paraffin industry in Scotland bituminous shale is largely used for this purpose, and in Germany the deposits of brown coal are utilised The material is distilled by a continuous process in long vertical retorts constructed of iron and fireclay, yielding ammonia, inflammable gases and tar The latter after purification by washing with concentrated sulphuric acid and caustic soda (to remove creosote oil) is redistilled and separated into four fractions naphtha, paraffin oil, lubricating oil and paraffin wax Besides these, a product resembling asphalt may be left behind in the retort

Paraffin wax so obtained consists chiefly of higher members of the saturated hydrocarbons, together with those of the ethylene series (p 108), and according to its composition varies somewhat in appearance,

[1] F Fischer and Gluud, *J S C I*, 1919, 38, 563 A [2] F Fischer and Tropsch, *Ber*, 1926, 59, 830, 923 [3] A Spilker, *Zeit f ang Ch*, 1926, 39, 997

melting-point and boiling-point[1] The solid hydrocarbons, beginning with $C_{19}H_{40}$, separate in large transparent leaves higher in the series they become translucent and granular still higher they are opaque and wax-like solids The melting-points range from 31° to 110° and the boiling-points from about 300° upwards

As has already been shown by numerous investigations into the low temperature coking process, ordinary coal may also yield products of the nature of paraffin wax on dry distillation, and it has recently been demonstrated that solid paraffin is a typical constituent of the low-boiling tar produced in this manner

Reference has already been made to the occurrence of solid paraffins and isoparaffins in nature One of the most important deposits of this kind is the *ozokerite* or earth-wax of eastern Galicia The more or less solid product varies from yellow to black in colour, and is found in layers from 20 to 100 metres below the surface The raw material is refined by melting out from earthy impurities, and the brownish product is treated with caustic soda and sulphuric acid, decolorised by charcoal, and finally bleached The resulting wax-like substance is known as *ceresine*

Uses—Among the different paraffin waxes those which are hard enough are employed, either alone or admixed with the higher fatty acids, in the manufacture of candles Softer varieties are utilised in the match industry, for waterproofing fabrics and for dressing leather

Asphalt or mineral pitch has been known from earliest times (Trinidad, Cuba, West Indies, Alsace), and is an oxidation product of the higher boiling constituents of petroleum It is used in the manufacture of black varnishes, as a protective paint, as insulating material and in large amounts for the paving of roads

II.—UNSATURATED HYDROCARBONS

Nomenclature of the Open chain Unsaturated Hydrocarbons

Those hydrocarbons containing one double bond are named after the corresponding saturated compounds by changing the termination -ane into -ylene, or according to the Geneva proposals into -ene Should two or more pairs of doubly linked carbon atoms be present, this is indicated by the ending -diene, -triene, etc The position of the double bond is shown by prefixing the letter or number of the first atom of the doubly bound pair, *e g* —

$$H_2C\ \ CH_2 \qquad\qquad H_2C\ \ CH\ \ CH_2\ \ CH_2\ \ CH\ \ CH_2$$

Ethylene or ethene — Diallyl or $\alpha\epsilon$-hexadiene

If the double bond occurs between a carbon atom of the main chain and one of the side chain, the name of the main chain takes the termination -ane and that of the side chain ene

$$\begin{array}{c} H_3C\ \ CH_2\ \ C\ \ CH_2\ \ CH_3 \\ \quad\ \ CH_2 \end{array} \qquad\qquad \begin{array}{c} H_3C\ \ CH_2\ \ CH_2\ \ C\ \ CH_2\ \ CH_2\ \ CH_3 \\ \qquad\quad CH\ \ CH_3 \end{array}$$

γ Methene pentane — δ Ethene heptane

[1] For the oxidation of paraffin, see C Kelber, *Ber*, 1920, 53, 66, 1567

If the double bond occurs in the side chain the name of the latter takes the termination -enyl

$$\begin{array}{ccccccccc} \alpha & \beta & \gamma & \delta & \epsilon & & & & \\ H_3C & CH_2 & CH_2 & CH_2 & CH & CH_2 & CH_2 & CH_2 & CH_3 \\ & & & & \mid\ \epsilon^1 & \epsilon^2 & \epsilon^3 & & \\ & & & & CH & CH & CH_3 & & \end{array}$$

ϵ^1 Propenyl nonane

Similarly the names of hydrocarbons containing one or more triple bonds end in -ine, -diine, triine, etc

$CH\ C\ CH_3$	$CH\ C\ CH_2\ CH_2\ C\ CH$
Allylene or propine	Dipropargyl or $\alpha\zeta$ hexdiine

These compounds may also be described as alkyl derivatives of acetylene, *e g*, allylene or methyl acetylene

The names of hydrocarbons containing both double and triple bonds end in -enine, *e g*, $HC\ C\ CH_2\ CH\ CH_2$ is called $\alpha\delta$-pentenine

1 Olefines, or Hydrocarbons of the Ethylene Series

Those aliphatic hydrocarbons which differ by a deficiency of two hydrogen atoms from the corresponding paraffins, possess the general formula C_nH_{2n}, and take their name from ethylene, the first member of the series It should be noted that no compound corresponding to methylene, CH_2, is known to exist All the hydrocarbons of this group contain two of their carbon atoms linked together with a double bond (*e g*, $H_2C = CH_2$) which is consequently termed the ethylene bond Isomeric with the olefines are the cycloparaffins, also of the general formula C_nH_{2n}, but possessing a closed ring structure in place of the open chains of the ethylene series

The nomenclature of the olefines has been discussed above, but the simpler compounds are frequently designated as substituted ethylenes —

$H_3C\ CH\ CH\ CH_3$	$(H_3C)_2C\ CH_2$	$(H_3C)_2C\ C(CH_3)_2$
Symmetrical dimethyl ethylene	Unsymmetrical dimethyl ethylene	Tetramethyl ethylene

Properties—In their physical properties the olefines closely resemble the paraffins The lower members from C_2H_4 to C_4H_8 are gases, the intermediate ones are liquids and the highest are solids They burn with a smoky and very luminous flame The boiling-points of corresponding hydrocarbons of the two series lie very close together, but the melting-points of the olefines are a little lower than those of the paraffins Most of the olefines are readily soluble in alcohol and practically insoluble in water For the lower members the specific gravity at the melting point is 0 63, and rises with increasing molecular weight to the neighbourhood of 0 79

In their chemical behaviour, which differs very considerably from

that of the paraffins, the most characteristic property is that of addition. The double bond in these hydrocarbons is capable of taking up two monovalent atoms or groups, becoming converted into a single bond, with the formation of paraffins or their substitution products. These additive properties are found also in other classes of compounds and may therefore be treated a little more fully at this stage.

By union with hydrogen, the olefines are transformed into paraffins of the same number of carbon atoms:—

$$\underset{\text{Ethylene}}{H_2C{:}CH_2} + H_2 = \underset{\text{Ethane}}{H_3C{\cdot}CH_3}$$

Catalytic Hydrogenation.—The addition of hydrogen to ethylene hydrocarbons used to be carried out by heating with hydriodic acid and phosphorus, but is now effected more rapidly and conveniently by catalytic methods. Sabatier, Senderens and Mailhe found that hydrogen adds on directly to unsaturated compounds at a high temperature in the presence of finely divided nickel,[1] and the same change may be induced even more readily, without the addition of external heat, by the catalytic action of finely divided metals of the platinum group.[2] A detailed study has also been made of the reduction of unsaturated compounds, including ethylene, by gaseous hydrogen in the presence of colloidal palladium.[3] The results show that ethylene may be reduced to ethane at the ordinary temperature by treating equal volumes of ethylene and hydrogen with an aqueous solution of colloidal palladium. The hydrogenation is effected by the palladium hydrosol, which in the presence of hydrogen is converted into palladium hydrogen hydrosol, the latter then transferring its hydrogen to the dissolved ethylene. The process goes forward continuously as long as ethylene and hydrogen are both present in the mixture.

In general, catalytic hydrogenation finds frequent application in laboratory and factory for the reduction of unsaturated organic compounds with gaseous hydrogen (see hardening of fats, p. 193).

Olefines readily unite with chlorine, bromine, iodine and iodine chloride to form dihalogen derivatives:

$$H_2C{:}CH_2 + Br_2 = \underset{\text{Ethylene dibromide}}{CH_2Br{\cdot}CH_2Br}$$

The addition of hydrogen halides, of which hydriodic acid is the most reactive, leads to the production of alkyl halides. In this reaction, if it is possible for the addition to take place in more than one way,

[1] Sabatier and Mailhe, *J. C. S.*, 1907, A, i, 458, 488, 490, 549, 747. [2] Willstätter and Mayer, *Ber.*, 1908, 41, 1475. [3] Paal, *Ber.*, 1909, 42, 2239. Stark, *Ber.*, 1913, 46, 2335.

the halogen usually attaches itself to that carbon atom which is united to the smaller number of hydrogen atoms (Markownikoff),

$$H_2C{:}CH_2 + HI = \underset{\text{Ethyl iodide}}{H_3C{\cdot}CH_2I}$$

$$\underset{\substack{\text{Isobutylene}\\(\beta\text{ methyl propylene})}}{(H_3C)_2C{:}CH_2} + HI = \underset{\substack{\text{Tertiary butyl iodide}\\(\beta\text{ iodo }\beta\text{ methyl propane})}}{(H_3C)_2CI{\cdot}CH_3}$$

Aqueous hypochlorous acid converts the olefines into chlorohydrins (see also p. 237), in which case the hydroxyl group links itself preferably to the less hydrogenated carbon atom. Similar results are obtained with dilute chlorine water or bromine water[1] (Read).

$$CH_2{:}CH_2 + HO{\cdot}Cl = \underset{\text{Ethylene chlorohydrin}}{HOCH_2{\cdot}CH_2Cl}$$

$$\underset{\text{Isobutylene}}{(H_3C)_2C{:}CH_2} + HO{\cdot}Cl = \underset{\text{Isobutylene chlorohydrin}}{(CH_3)_2C(OH){\cdot}CH_2Cl}$$

The olefines also combine directly with nitrogen trioxide, nitrogen dioxide, nitrosyl chloride and nitrosyl bromide to form respectively nitrosites, nitrosates, nitroso chlorides and nitroso-bromides, *e.g.*

$$\underset{\text{Tetramethyl ethylene}}{(CH_3)_2C{:}C(CH_3)_2} + NOCl = \underset{\text{Tetramethyl ethylene nitroso chloride}}{(CH_3)_2C(Cl){-}C(NO)(CH_3)_2}$$

With concentrated sulphuric acid the olefines yield alkyl-sulphuric acids, also known as alkyl hydrogen sulphates, the acidic radical (*cf.* addition of hydrogen halide) attaching itself to that carbon atom united to the smaller number of hydrogen atoms[2]

$$H_2C{:}CH_2 + (HO)_2SO_2 = \underset{\text{Ethyl sulphuric acid}}{H_3C{\cdot}CH_2{\cdot}O(HO)SO_2}$$

$$(H_3C)_2C{:}CH_2 + (HO)_2SO_2 = \underset{\text{Isobutyl-sulphuric acid}}{(H_3C)_2C(OSO_3H){-}CH_3}$$

On boiling the alkyl-sulphuric acids in aqueous solution they decompose to form an alcohol and sulphuric acid:

$$C_2H_5O{\cdot}SO_2{\cdot}OH + HOH = C_2H_5OH + HO{\cdot}SO_2{\cdot}OH$$

[1] J. Read and co-workers, *J. C. S.*, 1920, 1214; 1922, 989; 1923, 715. [2] This reaction serves also for the separation of olefines from paraffins, the latter being scarcely affected: see Worstall, *J. Am. C. S.*, 1899, **21**, 245.

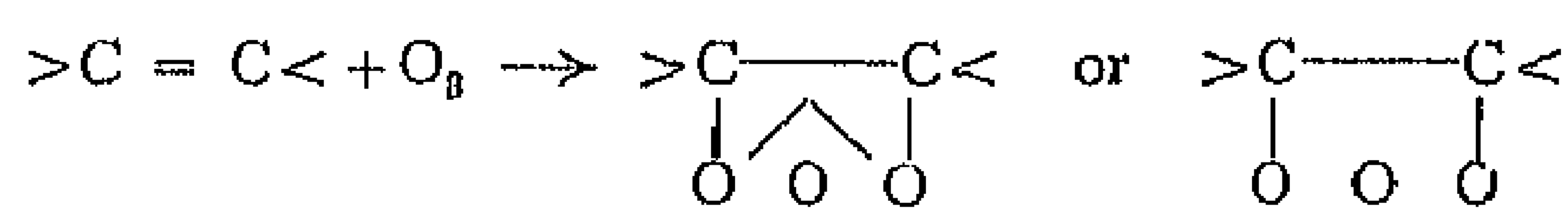
In this manner it is possible to effect the indirect addition of the elements of water to the olefines, converting them into alcohols

$$H_2C\ CH_2 + HOH = H_3C\ CH_2OH$$

Ethylene combines with fuming sulphuric acid to yield β-hydroxy-ethyl-sulphonic acid (isethionic acid), and with concentrated nitric acid to form β nitroethyl alcohol [1]

$$\underset{\text{Ethylene}}{H_2C\ CH_2} + HO\ NO_2 = \underset{\beta\text{ nitroethyl alcohol}}{HO\ CH_2\ CH_2\ NO_2}$$

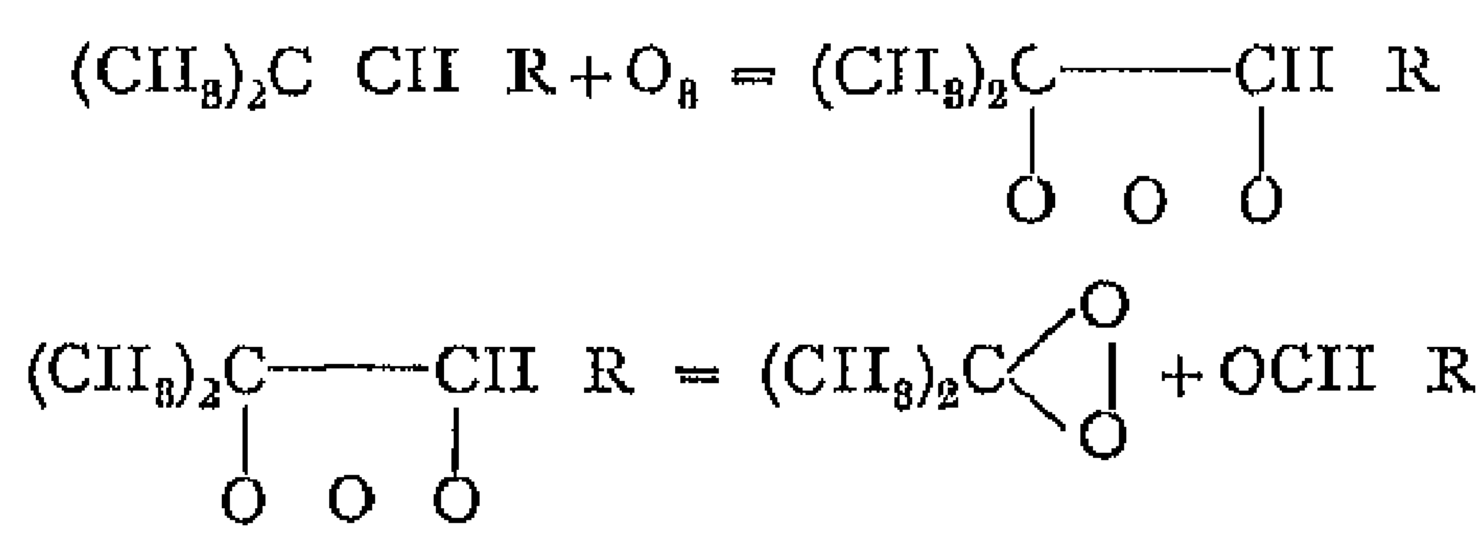
It has been shown by Harries [2] in a series of investigations, that if olefines and other unsaturated substances, either in the pure state or in aqueous solution, are treated with ozone, they form compounds containing a molecule of ozone attached to each double bond On warming these explosive ozonides with water, they are decomposed into aldehydes or ketones, and hydrogen peroxide,



Ozonide (O tetravalent) (O divalent)

$$+ H_2O \longrightarrow >CO + >CO + H_2O_2$$

or they may yield a peroxide and an aldehyde, as illustrated in the equation



Ozonide Peroxide Aldehyde

This reaction has been utilised by Harries in connection with the constitution of rubber

For the addition of mercaptans to olefines, see Posner, *Ber*, 1905, 38, 646, and of cuprous chloride to ethylene, Manchot and Brandt, *Ann*, 1909, 370, 286

Furthermore, the olefines are also capable of polymerisation, isobutylene, for example, being converted into di-isobutylene under the influence of dilute sulphuric acid, zinc chloride, or other reagents

$$(CH_3)_2C\ CH_2 + (CH_3)_2C\ CH_2 = (CH_3)_3C\ CH\ C(CH_3)_2$$

[1] Wieland and Sakellarios, *Ber*, 1920, 53, 201 [2] Harries, *Ann*, 1905, 343, 311, *Ber*, 1909, 42, 3305, *Ann*, 1910, 374, 288, *Ber*, 1912, 45, 936 For the constitution of ozonides, see H Staudinger, *Ber*, 1925, 58, 1088

When heated under pressure they yield naphthenes, thus affording experimental evidence for the hypothesis of Engler that the naphthenes in petroleum are derived from ethylene homologues[1]

The olefines are very easily oxidised Dilute alkaline permanganate solutions are decolorised by them, and the olefine converted into a dihydric alcohol

$$H_2C\ CH_2 \longrightarrow CH_2OH\ CH_2OH$$

On more vigorous oxidation (chromic acid, ozone) the chain is ruptured at the double bond, with the formation of aldehydes, ketones and acids

DETECTION OF THE ETHYLENE DOUBLE BOND

Two of the above reactions are of general use in testing for the presence of double bonds in unsaturated compounds, except in those containing certain ring systems to be described later

(a) *Baeyer's Permanganate Test*—According to Baeyer, alkaline permanganate is a general reagent for the recognition of unsaturated compounds The test is carried out in aqueous solution by addition of a little sodium carbonate or bicarbonate and a drop of potassium permanganate The colour of the latter rapidly disappears and a brown flocculent precipitate of a hydrated oxide of manganese forms The reaction may also be performed in alcoholic solution, in which case a blank test should first be carried out with alcohol and permanganate alone In the case of compounds such as aldehydes, which already possess reducing properties, the reaction obviously gives no information as to the presence or absence of double bonds

(b) *Addition of Bromine*—Unsaturated compounds frequently absorb bromine with great ease, as is shown by shaking them with bromine water, when the colour disappears (In very dilute aqueous solutions this yields bromohydrins, see p 110) It should be emphasised, however, that a number of substances are known, which, despite the presence of double bonds in the molecule, do not take up bromine[2]

FORMATION OF THE OLEFINES

The following methods are of general application

1 The dehydration of alcohols by means of concentrated sulphuric acid, phosphoric or oxalic acid, or zinc chloride

$$\underset{\text{Ethyl alcohol}}{H_3C\ CH_2\ OH} = \underset{\text{Ethylene}}{H_2C\ CH_2} + H_2O$$

Pure alumina has also been found to act as an energetic catalyst in splitting off the elements of water from alcohols, and olefines may be

[1] Engler and Routala, *Ber*, 1909, **42**, 4613, 4620 Ipatiew, *Ber*, 1911, **44**, 2978, 1913, **46**, 1748 [2] *Cf* Nef, *Ann*, 1897, **298**, 202 Bauer, *Ber*, 1904, **37**, 3317

prepared by passing the vapour of an alcohol over alumina heated to 300°[1]

Secondary and tertiary alcohols lose water more readily than the primary compounds

Many tertiary alcohols pass into unsaturated hydrocarbons with extraordinary ease, sometimes spontaneously at the moment of their formation, or merely on distillation For this reason olefines are frequently produced by the action of ketones on alkyl magnesium halides (see Grignard reaction), particularly when an excess of the latter is employed[2]

When sulphuric acid is used the reaction is often complicated by polymerisation of the olefine under influence of the acid Thus the formation of butylene, C_4H_8, is accompanied by the production of hydrocarbons of two or three times this molecular weight, viz, dibutylene, C_8H_{16}, and tributylene, $C_{12}H_{24}$

2 The action of alcoholic sodium or potassium hydroxide on the alkyl halides, particularly the iodides

$$C_nH_{2n+1}I + KOH = C_nH_{2n} + KI + H_2O$$

According to Sabatier and Mailhe,[3] finely divided metals (Ni, Cu, and Co), or anhydrous chlorides of divalent metals (Ni, Co, Cd, Fe, Pb, and Ba), possess the property of decomposing alkyl halides into hydrogen halide and the corresponding olefine

3 The electrolysis of concentrated aqueous solutions of the potassium salts of certain saturated dicarboxylic acids, *e g*, ethylene from potassium succinate

$$\begin{array}{l} H_2C\,CO_2K \\ \quad | \\ H_2C\,CO_2K \end{array} + \begin{array}{l} HOH \\ \\ HOH \end{array} = \begin{array}{l} H_2C \\ \quad \| \\ H_2C \end{array} + 2CO_2 + 2KOH + H_2$$

4 Olefines are often produced, together with paraffins, by the dry distillation of complex organic compounds, and hence ethylene is present in coal gas

Ethylene, ethene, $H_2C{=}CH_2$, occurs to the extent of 4 to 5 per cent in coal gas, and is usually prepared in the laboratory by heating one part of alcohol with four parts of concentrated sulphuric acid In order to prevent frothing, sufficient sand may be added to bring the mixture to a pasty consistency In this reaction ethylsulphuric acid is first formed, and on further heating breaks up into ethylene and sulphuric acid

$$C_2H_5OH + H_2SO_4 = C_2H_5SO_4H + H_2O\,, \quad C_2H_5SO_4H = C_2H_4 + H_2SO_4$$

The gas is purified by bubbling through sodium hydroxide and concentrated sulphuric acid, in order to remove traces of carbon dioxide, sulphur dioxide, alcohol and ether A less impure ethylene may be prepared by adding alcohol, drop by drop, to syrupy phosphoric acid heated to 220°

For further methods of formation see above

[1] Bouveault, *Bull Soc Chim* (4), 3, 117 [2] Klages, *Ber*, 1902, 35, 2633 Hell, *Ber*, 1904, 37, 225, 230, 453, 1429, 4188 [3] See Sabatier and Mailhe, *J C S*, 1908, A, i, 594, 713

Ethylene is a colourless gas possessing a faint ethereal smell; it is only slightly soluble in water, but more so in alcohol and ether. It burns with a luminous flame and forms an explosive mixture with oxygen. When led into bromine, rapid combination ensues with the formation of ethylene bromide, $C_2H_4Br_2$. Other properties of ethylene have been already described above. The oxidation of the gas by means of atmospheric oxygen has been examined by Willstätter and Bommer,[1] who found that formaldehyde was obtained in good yield.

$$CH_2\ CH_2 + O_2 = 2CH_2O$$

In view of the almost unlimited uses of formaldehyde, this reaction may yet prove of industrial importance.

Ethylene is now being utilised in an interesting manner in the fruit industry. When intended for transportation to considerable distances fruit is gathered and packed before it is fully ripe. On arrival at its final destination it is maintained for a few days in an atmosphere containing a small proportion of ethylene, which rapidly develops the colour and completes the ripening.

A few of the olefines, together with their boiling points, are quoted in the following list. As may be seen, isomerism first occurs in the case of butene. Stereoisomerism[2] may also occur (see p. 49).

Propene, C_3H_6 = $H_3C\ CH\ CH_2$, b.p. −40°

Butenes, C_4H_8 =
1. $H_3C\ CH_2\ CH\ CH_2$, ethyl ethylene, b.p. −5°
2. $H_3C\ CH\ CH\ CH_3$, *plane* sym. dimethyl-ethylene,[2] b.p. +1°
   axially sym. " b.p. +2.5°
3. $(H_3C)_2C\ CH_2$, unsym. dimethyl ethylene, b.p. −6°

Pentenes, C_5H_{10} =
1. $H_3C\ CH_2\ CH_2\ CH\ CH_2$, *n* propyl ethylene, or α amylene, b.p. +39°
2. $H_3C\ CH_2\ CH\ CH\ CH_3$, sym. methyl-ethyl ethylene, or β amylene, b.p. +36°
3. $\begin{matrix}H_3C\ CH_2 \\ CH_3\end{matrix}\!>\!C\ CH_2$, unsym. methyl ethyl ethylene, or γ amylene, b.p. +31°
4. $(H_3C)_2C\ CH\ CH_3$, trimethyl ethylene, or β isoamylene, b.p. +36°

Among the pentenes or amylenes, a mixture of which is obtained industrially by heating fusel oil with zinc chloride, trimethyl-ethylene or β-isoamylene is of special interest. It is employed under the name of *pental* as a narcotic of short duration, and also serves for the preparation of tertiary amyl alcohol.

2. Hydrocarbons, C_nH_{2n-2}

Under the above general formula are classed two groups of hydrocarbons, the diolefines containing two ethylene bonds in the molecule, and the acetylenes containing a triple bond, named after acetylene, $HC \equiv CH$, the first member of the series.

[1] Willstätter, *Z. ang. Ch.*, 1919, 32, 330. [2] For the stereoisomerism of the symmetrical dimethyl ethylenes, see Wislicenus, *Ann.*, 1900, 318, 207.

DIOLEFINES OR ALLYLENES

For the *nomenclature* of these compounds compare p. 107.

In *properties and chemical behaviour* the diolefines show many resemblances to the olefines, and differ from the acetylenes in forming no copper or silver compounds. On the other hand they give precipitates with a solution of mercuric chloride.

The manner in which hydrocarbons containing a conjugated double bond, $C=C—C=C$, unite with *two* monovalent atoms has already been discussed on pp. 23 and 24.

Formation.—Diolefines are obtained from the dibromo substitution products of the saturated hydrocarbons, by removing hydrogen bromide with alcoholic potash or quinoline;[1] by heating the phosphates of diamines;[2] and by the *exhaustive methylation* of certain cyclic bases (p. 647). Since these compounds have recently been employed in the technical preparation of artificial caoutchouc, various synthetic methods have been devised for their manufacture, which are given in more detail under caoutchouc.

Allene, $H_2C:C:CH_2$, may be prepared by the electrolysis of potassium itaconate, also from tribromo propane, $CH_2Br·CHBr·CH_2Br$, by removal of hydrogen bromide and bromine.

Butadiene, erythrene, 1.3-divinyl, $H_2C:CH·CH:CH_2$, is produced from erythritol by heating with formic acid, hence the name erythrene. A purer product may be obtained by the exhaustive methylation of N-methyl pyrrolidine. Harries has also prepared it in quantity from phenol.[3]

1.3-Pentadiene, *a*-**methyl butadiene, piperylene,** $H_2C:CH·CH:CH·CH_3$, is obtained in a similar manner from piperidine by exhaustive methylation.[1]

Isoprene, β-methyl-butadiene (β-methyl-divinyl), $H_2C:\underset{\displaystyle CH_3}{\underset{|}{C}}·CH:CH_2$,

is the most important hydrocarbon of this series. As it is produced together with trimethylethylene and dipentene by the dry distillation of caoutchouc,[5] it is of great importance in connection with the constitution of the latter. Isoprene may be prepared technically by various methods, *e.g.* from the isoamyl alcohol of fusel oil (p. 142) in the following stages:

$$\underset{\text{Isoamyl alcohol}}{(CH_3)_2CH·CH_2·CH_2OH} \xrightarrow{HCl} \underset{\text{Isoamyl chloride}}{(CH_3)_2CH·CH_2·CH_2Cl} \xrightarrow{Cl_2} \underset{\text{Dimethyl trimethylene chloride}}{(CH_3)_2CCl·CH_2·CH_2Cl}$$

$$\xrightarrow[\text{lime at 470}]{\text{over soda}} CH_2=\underset{\displaystyle CH_3}{\underset{|}{C}}—CH=CH_2$$

Isoprene is a liquid, b.p. 37°, which on heating to 300° under pressure yields dipentene. Under certain conditions it polymerises to caoutchouc (p. 353).

[1] Baeyer, *Ann.*, 278, 94; Markownikoff, *Ann.*, 1898, 302, 29. [2] Harries, *Ber.*, 1901, 34, 300. [3] Harries, *Ann.*, 1911, 383, 179. [4] For proof of the above formula see Thiele, *Ber.*, 1900, 33, 666. [5] Wallach, *Ann.*, 1885, 227, 295; Ipatiew, *J. Pr. Ch.* [2], 1897, 55, 4.

Isoprene is also of interest in connection with the chemistry of the carotinoids and the terpenes (p 484)

Butadienes, in general, combine quantitatively with acrylic aldehyde, maleic anhydride and other compounds containing the group $CH{:}CH{\cdot}CO$ to form hydroaromatic derivatives (*Diels and Alder*) This furnishes an important synthetic method of preparing cyclic compounds (see p 365)

The Acetylene Hydrocarbons

Nomenclature—In addition to the details given on p 108, it may be mentioned that compounds of this series are frequently named as substitution products of the first member, acetylene, $CH\equiv CH$, *e g*, 3-butine or ethyl-acetylene, $C_2H_5{\cdot}C\equiv CH$

Formation—1 They can generally be prepared from the mono-halogen substitution products, or the dihalogen addition products, of the ethylene hydrocarbons, by heating with alcoholic potash, *e g*

$$CH_2Br\cdot CH_2Br + 2KOH = CH\equiv CH + 2KBr + 2H_2O$$

An alcoholic solution of sodium or potassium ethoxide gives better yields, as there is then no tendency for the decomposition to stop at the intermediate stage of vinyl bromide

2 Aldehydes and ketones also serve for the preparation of the acetylenes With phosphorus pentachloride they are converted into dichloro-paraffins, which with potassium hydroxide yield acetylenes

$$\underset{\text{Acetone}}{CH_3\cdot CO\cdot CH_3} \longrightarrow \underset{\text{2-Dichloro propane}}{CH_3\cdot CCl_2\cdot CH_3} \longrightarrow \underset{\text{Methyl-acetylene}}{CH_3\cdot C\equiv CH}$$

3 Acetylene and its homologues are also formed by the dry distillation of organic compounds and are therefore present in coal gas

Properties and Chemical Behaviour—In physical respects the acetylenes resemble the paraffins and olefines The lower members of the series up to crotonylene, C_4H_6, are gases, then follow liquids and finally from $C_{16}H_{30}$ upwards they are solids

The chemical behaviour of the acetylenes shows them to be strongly unsaturated They unite readily with hydrogen, halogens and hydrogen halides, in two stages, each of which corresponds to the addition of one molecule of these substances If two molecules of halogen acid are

$$CH\equiv CH \xrightarrow{HBr} \underset{\text{Vinyl bromide}}{CH_2{:}CHBr} \xrightarrow{HBr} \underset{\text{Ethylidene bromide}}{CH_3\cdot CHBr_2}$$

taken up, both halogen atoms attach themselves to the same carbon atom Under certain conditions *polymerisation* may take place, *e g* acetylene, C_2H_2, polymerises to form benzene, C_6H_6, and dimethyl-acetylene, C_4H_6, to hexamethyl-benzene, $C_{12}H_{18}$ This is an important method of passing from the aliphatic to the aromatic series, and the

acetylene condensation is to be regarded as the main, though not the only, source of aromatic compounds in coal tar[1]

A characteristic of acetylene and its monoalkyl-substitution products, R C CH, is the property of giving solid crystalline precipitates with ammoniacal solutions of silver or cuprous salts In this reaction the hydrogen of the group, $\equiv CH$, is substituted by metals to form acetylides of the type of copper acetylide, C_2Cu_2, which are explosive and regenerate the original hydrocarbon on warming with hydrochloric acid By means of these metallic compounds acetylene may be purified and separated from other hydrocarbons Besides these salts in which acetylene appears to function as an acid, there are additive compounds known, *e g* CuCl, C_2H_2, produced by bringing acetylene into contact with the metallic salt[2]

ACETYLENE, ETHINE, $CH\equiv CH$

Preparation—Acetylene is readily prepared by dropping water on calcium carbide

$$CaC_2 + 2H_2O = Ca(OH)_2 + C_2H_2$$

The carbide is obtained industrially by heating quicklime with coke in an electric furnace, when the chief reaction takes place according to the equation

$$CaO + 3C = CaC_2 + CO$$

Certain other products are also formed from impurities in the lime, chiefly calcium phosphide from phosphates and ferrosilicon from iron and sand

The acetylene evolved from the technical product is contaminated with ammonia, hydrogen sulphide and especially phosphine Purification may be effected by washing with water to extract the ammonia, passing the gas over lime or hydrated iron ore to absorb hydrogen sulphide, and finally removing phosphine by means of bleaching powder, "heratol" (a mixture containing potassium bichromate and sulphuric acid), or other suitable oxidising mixtures

The preparation of acetylene from calcium carbide in the laboratory is most conveniently carried out by placing the carbide in a dry flask, fitted with a separating funnel and a delivery tube, and allowing water to run in drop by drop from the funnel

In addition to the methods of formation given above in the general section, acetylene is also produced by the following reactions

It may be synthesised from its elements (Berthelot) by causing an electric arc to pass between two carbon electrodes in an atmosphere of hydrogen

$$2C + 2H = CH \quad CH$$

It is also formed by electrolysing solutions of the alkali salts of fumaric and maleic acids

[1] Further pyrogenic acetylene condensations have been described by R Meyer, see *Ber* 1912, 45 1609 [2] Manchot, Withers and Oltrogge, *Ann*, 1912, 387, 257

Acetylene [illegible]
and [illegible]
volume [illegible]
conduct [illegible]
which [illegible]
[illegible]

Propert[illegible]
ethereal [illegible]
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an endothermic [illegible]
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Acetylene when [illegible]
flame and the [illegible]
burnt at a jet under [illegible]
of water, the flame [illegible]
required [illegible]
jets which [illegible]
oxygen the [illegible]

Under the [illegible]
molecules [illegible]
formed also [illegible]
reaction forms [illegible]
over heated cataly[illegible]
benzene, naphthalene and [illegible]

As mentioned above [illegible]
able by metals and the [illegible]
may be utilised for the [illegible]
the dry state the [illegible]
explosive. Under the [illegible]
combines with water [illegible]
oxidised to give [illegible]

[illegible]

been developed on the large scale, and adapted with great success to the manufacture of acetic acid

Diacetylene, HC C C CH, may be prepared from copper acetylide by oxidation with hot aqueous cupric chloride, and decomposing the copper derivative so obtained with dilute mineral acid It boils at 10° under 760 mm and polymerises with great ease

II

Halogen Derivatives of the Hydrocarbons

The halogen derivatives of the hydrocarbons provide the most valuable starting material for the synthesis of organic compounds, and if only for this reason merit description in some detail In addition it may be noted that several of them, such as chloroform, $CHCl_3$, and iodoform, CHI_3, are extensively used in medicine

I—HALOGEN DERIVATIVES OF THE PARAFFINS.

Halogens normally function as monovalent elements, and a hydrocarbon such as methane would therefore be expected to yield four chlorine derivatives, CH_3Cl, CH_2Cl_2, $CHCl_3$ and CCl_4, as well as four bromine, iodine and fluorine compounds Ethane, however, gives rise to nine instead of six chloro-derivatives, since in this case position isomerism is possible (*cf* p 20)

Methods of Formation—1 The monohalogen derivatives or alkyl halides are most conveniently prepared from the corresponding alcohols, by replacing the hydroxyl group of the latter with halogen, either by the action of halogen acids,

$$\underset{\text{Ethyl alcohol}}{C_2H_5 \cdot OH} + HBr = \underset{\text{Ethyl bromide}}{C_2H_5 \cdot Br} + H_2O$$

or of halogen compounds of phosphorus,

$$3C_2H_5 \cdot OH + PI_3 = \underset{\text{Ethyl iodide}}{3C_2H_5 \cdot I} + H_3PO_3$$

In the latter case, at all events in introducing bromine and iodine, it is not always necessary to employ previously prepared phosphorus halide, this being usually formed during the course of the reaction For example, ethyl iodide may be obtained by adding powdered iodine to a mixture of alcohol and red phosphorus, and warming to complete the reaction

2 Alkyl halides are readily prepared by treating an aqueous solution of a metallic halide with dimethyl or diethyl sulphate In this case only one of the alkyl groups takes part in the reaction, *e g*

$$\underset{\substack{\text{Dimethyl}\\\text{sulphate}}}{SO_4(CH_3)_2} + KI = \underset{\substack{\text{Methyl}\\\text{iodide}}}{CH_3I} + \underset{\substack{\text{Potassium}\\\text{methyl sulphate}}}{SO_4K(CH_3)}$$

3. Halogen deriv[illegible] on the paraffin[illegible] preparation [illegible] separable mixt[illegible] Chloride, [illegible] $CHCl_3$ and [illegible] in sunlight [illegible] *chlorine* [illegible] warmed [illegible] hydrocarbons [illegible] such a [illegible] hydriodic acid [illegible]

4. As has been [illegible] the olefine and [illegible] halides to form [illegible]

5. On treating [illegible] chloride the [illegible] yield dichloro[illegible]

[illegible]

6. It has recently been [illegible] may be obtained [illegible] pentachloride or [illegible] warming with phosphorus [illegible] 1 : 5-dibromopentane [illegible]

7. Alkyl chlorides may [illegible] leading a mixture of hydrogen [illegible] 450° over aluminium [illegible] the isomeric alkyl chloride [illegible] is obtained [illegible] with a [illegible] acid [illegible]

The preparation [illegible] conveniently effected by [illegible] acetone solution.

Properties. A few of the [illegible] gaseous under ordinary [illegible] sweet smelling liquids [illegible] The iodo compounds are [illegible] darken on standing, particularly [illegible] decomposition occurs with [illegible]

[1] J. v. Braun, Ber. 1904, 37, [illegible] converted into [illegible] 4541; 1911, 44, 1464 [illegible] 1910, 43, 1318

be minimised by the addition of some mercury, or a little finely divided ("molecular") silver. Among similarly constituted compounds, the chlorides possess the lowest boiling point, the corresponding bromides boil approximately 25°, and the iodides 50°, higher than the chlorides. The iodides also possess the highest and the chlorides the lowest specific gravity, the figure sinking in each case as the hydrocarbon radical increases in magnitude. The halogen derivatives are not soluble in water, but dissolve readily in organic solvents such as alcohol, ether or carbon disulphide.

At low temperatures chlorine reacts with methyl or ethyl iodide to form an iodochloride, $CH_3 \cdot ICl_2$ or $C_2H_5 \cdot ICl_2$. Ethyl iodochloride decomposes in the neighbourhood of −36°.

With regard to the *chemical properties* of the alkyl halides, it should be noted that, in spite of certain resemblances to the metallic halides, they differ characteristically from the latter in their behaviour towards silver nitrate. As is well known, the metallic halides such as potassium iodide are ionised in solution, and react instantaneously with aqueous or alcoholic silver nitrate, all the halogen being precipitated as insoluble silver halide. The halogen substitution products of the hydrocarbons, on the other hand, are non-electrolytes, and either do not react with silver nitrate or the reaction sets in gradually. Pure chloroform, for example, may be shaken with aqueous silver nitrate without any separation of silver chloride, while ethyl iodide only very slowly yields a precipitate of silver iodide.

It must not be concluded from this behaviour with silver nitrate that the halogen is particularly firmly bound in the substituted aliphatic hydrocarbons, since by means of suitable reagents it is readily eliminated and replaced by hydroxyl, alkoxyl, amino or other groups. On this ease of reaction depends the extraordinary utility of the halogen derivatives, and especially the alkyl iodides, for organic synthesis. The latter are of great value in introducing alkyl groups into organic compounds, a process described in a later chapter.

In order to replace hydrogen in the hydroxyl group of an alcohol or acid by an alkyl radical, the sodium derivative of the alcohol or the silver salt of the acid may be heated with alkyl iodide. In some cases thallous salts of the acids give even better results.[1]

$$\underset{\text{Sodium ethoxide}}{C_2H_5 \cdot ONa} + C_2H_5I = \underset{\text{Diethyl ether}}{C_2H_5 \cdot O \cdot C_2H_5} + NaI$$

$$\underset{\text{Silver acetate}}{CH_3 \cdot COOAg} + C_2H_5I = \underset{\text{Ethyl acetate}}{CH_3 \cdot COOC_2H_5} + AgI$$

In a similar manner it is possible to replace a hydrogen atom attached to nitrogen or carbon, e.g.

$$NH_3 + CH_3I = \underset{\text{Methylamine}}{CH_3 \cdot NH_2} + HI, \quad \underset{\text{Aniline}}{C_6H_5 \cdot NH_2} + 2CH_3I = \underset{\text{Dimethyl aniline}}{C_6H_5N(CH_3)_2} + 2HI$$

[1] G. H. Christie and R. C. Menzies, *J. C. S.*, 1925, **127**, 2369; C. M. Fear and R. C. Menzies, *J. C. S.*, 1926, 937.

By means of the Wurtz synthesis an iodine atom may be exchanged for an alkyl group,

$$\underset{\text{Ethyl iodide}}{C_2H_5I + C_2H_5I} + 2Na = \underset{\text{Butane}}{C_2H_5 \cdot C_2H_5} + 2NaI$$

The preparation of unsaturated hydrocarbons from alkyl halides has already been referred to on pp 113, 116

It will also be seen later that the alkyl halides have been extensively applied to the preparation of organo metallic compounds particularly those of zinc and magnesium (p 127)

A final indication of the many-sided reactivity of the alkyl halides is given by their power of forming addition compounds with other substances, such as tertiary amines

$$\underset{\text{Pyridine}}{C_5H_5N} + CH_3I = \underset{\text{Pyridine methiodide}}{C_5H_5N{<}^{I}_{CH_3}}$$

Among the large number of substitution products of the paraffins known, the following are briefly described

Chloro-methane, methyl chloride, CH_3Cl, is prepared by heating a mixture of methyl alcohol and hydrochloric acid with zinc chloride, also by heating trimethylamine hydrochloride, $N(CH_3)_3HCl$, obtained from the residual liquors in sugar manufacture, to 360° It is a colourless, sweet-smelling gas which burns with a green edged flame, and on being cooled condenses to a liquid, b p −23° It comes on to the market in liquid form, and owing to the intense heat absorption resulting from its rapid evaporation, it is used for the production of low temperatures **Ethyl chloride**, b p +12°, is for the same reason employed as a local anæsthetic

Iodo-methane, methyl iodide, CH_3I, may be prepared from methyl alcohol, iodine, and red phosphorus It is a liquid of pleasant ethereal odour, b p 44° and sp gr 2 27 at 25° Under the influence of light it gradually darkens, owing to the separation of iodine

Iodo-ethane, ethyl iodide, C_2H_5I, is prepared from ethyl alcohol, iodine and red phosphorus Boiling-point 72 5° and sp gr 1 975

Ethylene bromide, CH_2Br-CH_2Br, is obtained by passing ethylene gas into bromine It is a colourless liquid of pleasant smell, boiling at 131° and solidifying at +8° It is much employed as a solvent and for synthetic purposes

Trichloro-methane, chloroform, $CHCl_3$, is a chlorination product of methane or methyl chloride, and is formed by the action of bleaching powder on various organic substances such as alcohol, acetone, acetic acid and its salts, and tartaric acid

The *method of preparation*, also used on the technical scale, is to distil aqueous alcohol with bleaching powder It is supposed that the first step in this reaction is the oxidation of alcohol to aldehyde, which

next undergoes substitution to trichloroaldehyde (chloral), this being then hydrolysed by the lime present in the bleaching powder to formic acid and chloroform,

$$CH_3\cdot CH_2\cdot OH \rightarrow \underset{\text{Acetaldehyde}}{CH_3\cdot C\begin{smallmatrix}\nearrow O\\ \searrow H\end{smallmatrix}} \rightarrow \underset{\text{Chloral}}{CCl_3\cdot C\begin{smallmatrix}\nearrow O\\ \searrow H\end{smallmatrix}} \rightarrow \underset{\text{Chloroform}}{CHCl_3} + \underset{\text{Formic acid}}{HC\begin{smallmatrix}\nearrow O\\ \searrow OH\end{smallmatrix}}$$

Ethyl alcohol

Acetone may be used instead of alcohol in this preparation

It is also possible to prepare chloroform by the electrolysis of a solution of potassium or calcium chloride in dilute aqueous alcohol or acetone[1] The primary reaction consists in the formation of a hypochlorite and proceeds according to the equation

$$\underset{\text{Acetone}}{CH_3\cdot CO\cdot CH_3} + 3HOCl = \underset{\text{Chloroform}}{CHCl_3} + \underset{\text{Acetic acid}}{CH_3COOH} + 2H_2O$$

Chloroform prepared by any of the above methods is generally impure It may be obtained in a very pure state, although at considerably greater expense, from chloral hydrate, which on heating with alkali decomposes into chloroform and the alkali salt of formic acid

$$CCl_3\cdot CHO + KOH = CHCl_3 + HCO_2K$$

Properties—Chloroform is a colourless mobile liquid, b p 62° and sp gr 1 491 at 17° It possesses a sickly sweet smell and a burning taste, dissolves readily in alcohol and ether, and is sparingly soluble in water

Inhalation of its vapour brings about loss of consciousness, and for this reason it is largely used as an anæsthetic in surgical operations Chloroform was discovered almost simultaneously by Liebig and Soubeiran in 1831, but its anæsthetic properties remained unknown till their discovery in Edinburgh by Simpson in the year 1848

Chloroform comparatively readily undergoes chemical changes Under the influence of air and light it decomposes into chlorine, hydrochloric acid and carbonyl chloride, $COCl_2$ The specially purified chloroform used for anæsthetic purposes is treated with a small amount —about 1 per cent—of alcohol, and preserved in a dark bottle filled to the stopper, under which conditions the above decomposition is arrested Chloroform reacts with chlorine to form carbon tetrachloride, CCl_4, when reduced with zinc and hydrochloric acid it yields methylene chloride, CH_2Cl_2 Concentrated nitric acid replaces the hydrogen atom with a nitro group, forming **chloropicrin**, CCl_3NO_2 When heated with aqueous or alcoholic potash, potassium formate is produced

$$CHCl_3 + 4KOH = \underset{\text{Potassium formate}}{HCO_2K} + 3KCl + 2H_2O$$

Chloroform may be tested for by warming with a primary amine (usually aniline) and alcoholic potash An isonitrile is thus formed

[1] J Feyer, *Z Elek*, 1919, 25, 115

possessing a characteristically unpleasant odour This reaction may be employed for the detection of primary amines as well as of chloroform

$$\underset{\text{Aniline}}{C_6H_5NH_2} + CHCl_3 + 3KOH = \underset{\text{Phenyl carbamine}}{C_6H_5NC} + 3KCl + 3H_2O$$

Tests for Purity—Chloroform for anæsthetic purposes must be of the highest grade of purity When shaken with water, the aqueous layer should not become acid, or give any cloudiness with silver nitrate

Bromoform, tribromomethane, $CHBr_3$, is prepared in a similar manner to chloroform by the action of bromine on alcohol or acetone, and is a liquid, boiling at 151°

Iodoform, triiodomethane, CHI_3, is produced by the action of iodine and caustic potash on alcohol, acetaldehyde or acetone, and in general any compound containing the group CH_3 CH(OH) C— or CH_3 CO C—

Technically it is prepared by warming a mixture of iodine, alcohol, and caustic potash or potassium carbonate

$$C_2H_5OH + 8I + 6KOH = CHI_3 + \underset{\text{Potassium formate}}{HCO_2K} + 5KI + 5H_2O$$

Acetone may also be used in place of alcohol as starting material

A modern method of preparation is by the electrolysis of an aqueous alcoholic solution of potassium iodide and carbonate[1]

Properties—Iodoform crystallises in yellow hexagonal plates of characteristic smell, it melts at 119°, readily sublimes and is volatile with steam It is insoluble in water, but soluble in alcohol and ether On treatment with an alcoholic solution of potassium ethoxide, or on reduction with hydriodic acid and phosphorus, methylene iodide, CH_2I_2, is formed Iodoform is extensively used in surgery as an antiseptic

Carbon tetrachloride, tetrachloromethane, CCl_4, is obtained as a colourless liquid, b p 76°, by the action of chlorine on chloroform or carbon bisulphide. It is largely used as a solvent Technically, the chlorination of carbon bisulphide is effected with the aid of aluminium chloride or manganese chloride as catalyst

A series of chlorinated compounds, all prepared from acetylene, have recently come into use as valuable non-inflammable solvents These polyhalogen derivatives are far less reactive than the mono-halogenated compounds

Acetylene tetrachloride, tetrachloroethane, $CHCl_2$ $CHCl_2$, is obtained by the addition of chlorine to acetylene in the presence of infusorial earth (*kieselguhr*) or other diluent, in the absence of which combination occurs explosively It is a heavy non-inflammable liquid, b p 147°, sp gr 1 601 at 15°, which is used technically under the name of *Westron* as a solvent for cellulose acetate varnishes, for rubber and fats, and also as an insecticide

[1] *C*, 1897, II, 695, 1898, I, 31, 1900, II, 719, *J Phys Ch*, 1903, 7, 84 Foyer, *Z Elek*, 1919, 25, 115

When the vapour of acetylene tetrachloride is passed over a catalyst ($BaCl_2$ or ThO_2) at 350°, one molecule of HCl is lost and **trichloro-ethylene**, *Westrosol*, CCl_2 CHCl, b p 87°, sp gr 1 471 at 15°, is formed This is used industrially for the extraction of oils from seeds, and for dry cleaning The halogen in trichloro-ethylene is very stable, and is not attacked by the common metals, even in the presence of moisture

Acetylene dichloride, *dichloro-ethylene*, CHCl CHCl, sp gr 1 278 at 15°, is prepared industrially as a mixture of two isomerides (b p 48° and 60°) by treating *Westron* with zinc in the presence of water

$$CHCl_2\ CHCl_2 + Zn = CHCl\ CHCl + ZnCl_2$$

It is used for extractions in place of ether or light petroleum The hot vapours may be ignited but the flame rapidly extinguishes itself

Carbon hexachloride, *hexachloroethane*, C_2Cl_6, is a solid, melting at 187°

II —HALOGEN DERIVATIVES OF THE UNSATURATED HYDROCARBONS

Only in exceptional cases are these compounds produced directly by the action of halogens on unsaturated hydrocarbons, since the first action of the halogen is generally to form an addition compound and not to substitute[1] We can, however, obtain the desired derivatives from these addition products by the partial removal of hydrogen halide with alcoholic potash, for example

$$H_2C\ CH_2 \xrightarrow{+Br_2} H_2CBr\ CH_2Br \xrightarrow{-HBr} \underset{\text{Vinyl bromide}}{H_2C\ CHBr},$$

$$\underset{\text{Sym tetrabromoethane}}{HCBr_2\ CHBr_2} \xrightarrow{-HBr} \underset{\text{Tribromoethylene}}{HCBr\ CBr_2} \xrightarrow{-HBr} \underset{\text{Dibromoacetylene [2]}}{CBr\ CBr}$$

The halogen derivatives of the olefines, in which halogen is united to a doubly bound carbon atom, differ markedly from the corresponding paraffin derivatives in that the halogen is in general not replaceable by other radicals such as hydroxyl Like the olefines themselves, they readily combine with halogens and halogen acids, and exist in geometrically isomeric forms (p 49)

Those halogen derivatives of the olefines in which, as in allyl iodide, H_2C CH CH_2I, the halogen is attached to a singly bound carbon atom, resemble the paraffin compounds in the reactivity of the halogen

The halogen derivatives of the acetylenes, like other acetylene compounds, are very unstable and readily undergo explosive decomposition, they also show a strong tendency to polymerise

[1] *Cf* Biltz and Küpper, *Ber*, 1904, **37**, 4412, for the substitution of hydrogen by iodine, by use of iodine and sodium hypoiodite [2] *C*, 1903, **II**, 102

Vinyl chloride,[1] monochloroethylene, $CH_2:CHCl$, is gaseous at ordinary temperatures Vinyl bromide boils at 16°

Allyl iodide, $H_2C:CH\cdot CH_2I$, may be obtained from allyl alcohol, or more simply from glycerol, by heating with hydriodic acid, or with iodine and phosphorus It is a colourless liquid, b p 102°, which smells of leeks, and occurs in the combined state in mustard oil and oil of garlic It is frequently employed in syntheses for the introduction of the allyl group

Tetraiodo ethylene, $CI_2:CI_2$, is obtained in lemon yellow crystals, m p 187°, when calcium carbide is added to a solution of iodine in potassium iodide at 0° It is odourless and possesses antiseptic properties

$$C_2Ca + 6I = C_2I_4 + CaI_2$$

Diiodo acetylene, $CI \vdots CI$, is also formed during the above reaction It crystallises in colourless needles, m p 78°, and is very volatile The vapour strongly attacks the mucous membranes

$$C_2Ca + 4I = C_2I_2 + CaI_2$$

For other *chloro-derivatives of acetylene* see previous page

III

Organo-metallic Compounds

The organo-metallic compounds are usually prepared by the action of metals, such as zinc, magnesium or mercury, on the alkyl iodides, and owing to their reactivity are frequently employed in synthetic reactions The zinc and magnesium compounds are the most important of this class, and it is only recently that the simpler derivatives of the alkali metals have been carefully studied

Sodium alkyls, *e g* sodium methyl, $NaCH_3$, are obtained by the action of sodium on the corresponding mercury alkyls[2] In the pure state they form colourless amorphous solids which are completely insoluble in indifferent solvents, and when heated decompose without melting They are extremely sensitive towards oxygen, moisture and carbon dioxide, are inflammable in air and very reactive[3]

Zinc alkyls were discovered in 1849 by Frankland They are obtained by the action of excess of zinc on alkyl iodides, zinc alkyl iodides being first formed which decompose into zinc alkyls and zinc iodide on further heating

$$C_2H_5I + Zn = C_2H_5ZnI, \quad 2C_2H_5ZnI = Zn(C_2H_5)_2 + ZnI_2$$

[1] The radical $H_2C{=}CH—$ is known as vinyl [2] W Schlenk and Holtz, *Ber*, 1917, 50, 262 [3] Schorigin, *Ber*, 1908, 41, 2717, 1910, 43, 1931 Schlubach, *Ber*., 1919, 52, 1910

The zinc alkyls are colourless, unpleasant smelling liquids which boil without decomposition at relatively low temperatures. They are spontaneously inflammable in air, and produce painful burns if brought into contact with the skin. Consequently they must be handled with caution.

Zinc methyl, $Zn(CH_3)_2$, b.p. 46°; *zinc ethyl*, $Zn(C_2H_5)_2$, b.p. 118°; *zinc propyl*, $Zn(C_3H_7)_2$, b.p. 146°.

As will be seen later, they may be employed in the synthesis of a variety of compounds, including alcohols and ketones (p. 168).

With water they decompose to form paraffins and zinc hydroxide:

$$Zn(CH_3)_2 + 2H_2O = Zn(OH)_2 + 2CH_4$$

Paraffins are also produced on heating zinc alkyls to a high temperature with alkyl iodides:

$$Zn(CH_3)_2 + 2CH_3I = ZnI_2 + 2H_3C \cdot CH_3$$

Organo-magnesium Compounds

The magnesium alkyls of the general formula MgR_2 have been specially investigated by Lothar Meyer and his pupils. Like the zinc compounds they are very reactive, but differ in being infusible solids which are non-volatile and insoluble in the common solvents. For this reason they are very inconvenient to work with and have been little employed in synthetic chemistry.

It is only in recent times, with the discovery that free magnesium alkyls could be replaced by the readily soluble compounds of the type RMgI, that the organo-magnesium derivatives have been used with such great success in synthesis.

It was shown by Grignard,[1] in a series of publications, that magnesium in the presence of dry ether interacts with numerous organic halogen compounds, particularly alkyl iodides and bromides, to form compounds of the above type which remain dissolved in the ether. At the same time it was found that the magnesium alkyl halides did not require to be isolated for synthetic purposes, but could be used directly in ethereal solution. They are solids and are not spontaneously inflammable in air.

Reactions between metallic magnesium and alkyl or aryl halides in ethereal solution are known as Grignard reactions, and compounds of the general formula R · Mg · Hal as organo-magnesium halides.

It was shown later by Tschelinzeff[2] that the formation of these compounds also takes place slowly in other solvents such as benzene, toluene and xylene, in the presence of a trace of ether. The amount of organo-magnesium halide formed is out of all proportion to the quantity of ether employed, from which it was concluded that in the

[1] Grignard, *Annales de l'Université de Lyon*, 1901, pp. 1 to 116. [2] Tschelinzeff, *Ber.*, 1904, 37, 4534.

Grignard reaction the ether plays the part of a *catalyst*[1] The formation of magnesium methyl iodide may be expressed by the following equations, in which the intermediate existence of an "oxonium salt" containing tetravalent oxygen is assumed

$$\text{I.}\qquad \underset{\substack{\text{Methyl}\\\text{iodide}}}{H_3CI} + \underset{\substack{\text{Diethyl}\\\text{ether}}}{(C_2H_5)_2O} = \underset{\substack{\text{Hypothetical inter}\\\text{mediate product}}}{\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!O\!<\!\!\begin{matrix}CH_3\\I\end{matrix}}$$

$$\text{II}\qquad (C_2H_5)_2O\ CH_3I + Mg = \underset{\substack{\text{Methyl mag-}\\\text{nesium iodide}}}{CH_3MgI} + \underset{\substack{\text{Diethyl}\\\text{ether}}}{(C_2H_5)_2O}$$

Tschelinzeff also found that other substances could act as catalysts The formation of organo-magnesium compounds takes place in solvents such as benzene, toluene, xylene and petroleum ether, when a few drops of a tertiary amine (*e g* dimethyl-aniline) are added In this case the magnesium compound is thrown out of solution as a white flocculent precipitate corresponding to the formula R Mg Hal This is sometimes of practical as well as theoretical importance, since the catalytic influence of the tertiary amine is in some cases far more energetic than that of ether, and the reaction often takes place more rapidly and with as good a yield as by the Grignard method Nevertheless, Grignard's method of preparing the compounds in dry ether solution is generally more convenient If desired, the magnesium alkyl halides may be isolated in combination with two molecules of ether, *e g* CH_3MgI, $2(C_2H_5)_2O$ According to Meisenheimer these compounds are regarded as complexes of magnesium in which the metal occurs as the central atom with a co-ordination number 4

$$\begin{matrix}(C_2H_5)_2O\\(C_2H_5)_2O\end{matrix}\quad Mg\!<\!\!\begin{matrix}CH_3\\I\end{matrix}$$

By reason of their extraordinary reactivity the organo-magnesium compounds aroused great interest, and the original investigations of Grignard were immediately followed by those of a number of other workers It was soon apparent that for synthetic purposes magnesium compounds of the type R Mg Hal were more conveniently manipulated, gave better yields, and were of more general utility than the zinc alkyls Already they have attained a position in synthetic chemistry unrivalled by that of any other class of compound.

With the aid of the Grignard reaction it is possible to synthesise hydrocarbons, primary, secondary and tertiary alcohols, ethers, ketones, aldehydes, carboxy- and thio-acids, phenols and thiophenols, and a variety of nitrogen compounds, as well as other alkyl metallic derivatives

[1] A chemical process, the velocity of which depends greatly upon the presence of some particular substance which is not itself used up in the chemical change, is termed a *catalytic reaction*, the substance in question being known as a *catalyst*

In addition to the above compounds, *alkyl derivatives of beryllium, aluminium, thallium, cadmium, mercury, lead, tin,*[1] *arsenic, silver* and *gold*[2] have also been prepared The mercury compounds HgR_2 are extremely poisonous liquids

The **lead alkyls**, *e g* lead tetramethyl, $Pb(CH_3)_4$, possess a special interest as illustrating the tetravalency of lead They are most conveniently obtained by acting on alkyl magnesium halides with lead chloride[3]

$$2PbCl_2 + 4CH_3MgI = Pb + Pb(CH_3)_4 + 4MgICl$$

Unsaturated organic compounds of lead, in which the lead atom appears to be united to carbon groups by less than four valency bonds, are formed by the action of alkyl halides on lead sodium amalgam, by the electrolytic reduction of ketones at lead cathodes,[4] and by the action of certain alkyl magnesium halides on lead chloride[5] The most interesting of these compounds are the lead triaryls,[6] $PbAr_3$, which correspond to triphenylmethyl (p 508)

Methyl dichloroarsine,[7] CH_3AsCl_2, has been used in warfare as a poison gas By the methylation of sodium arsenite with dimethyl sulphate at 85°, disodium methyl arsenite, $Na_2CH_3AsO_3$, is formed The latter on treatment with sulphurous acid is converted into methyl arsine oxide, which interacts with gaseous hydrochloric acid to give methyl dichloroarsine It may be separated from admixed methyl alcohol and hydrochloric acid by fractional distillation, and boils at 130° to 132°

IV

The Alcohols

Classification—The alcohols may be derived theoretically from the hydrocarbons by replacing a hydrogen atom of the latter by a hydroxyl group Generally speaking, therefore, they may be regarded as alkyl hydroxides (in which the alkyl radical may be saturated or unsaturated) with a constitution resembling that of the metallic hydroxides At the same time it should be emphasised that in their typical properties alcohols and inorganic bases show considerable differences The inorganic bases are electrolytes and alkaline in reaction, the alcohols

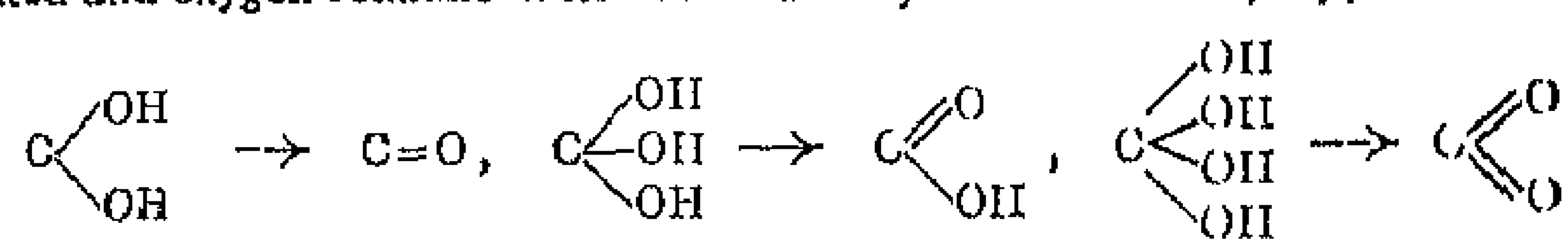
[1] For alkyl compounds of tin see Pope and Peachey, *Proc. Chem Soc*, 1903, **19**, 290, and P Pfeiffer, *Ber*, 1911, **44**, 1269, for organic silicon compounds see G Martin, *Ber*, 1913, **46**, 3289 [2] Pope and Gibson, *J C S*, 1907, **91**, 2061 [3] P Pfeiffer, *Ber*, 1904, **37**, 319, 1125, 4618 Hibbert, *Ber*, 1906, **39**, 160 Hofmann and Wolfl, *Ber*, 1907, **40**, 2425 [4] Tafel, *Ber*, 1911, **44**, 323 [5] Grüttner and Krause, *Ber*, 1916, **49**, 1416 [6] Krause and Schmitz, *Ber*, 1919, **52**, 2165, Krause and Reissaus, *Ber*, 1922, **55**, 888 [7] Uhlinger and Cook, *J Ind and Eng Ch*, 1919, **11**, 105

are non-electrolytes and neutral. As will be seen later, both alcohols and bases react with acids with elimination of water.

Corresponding to mono- and polyacid bases we have mono- and polyhydric alcohols. If one hydrogen in a hydrocarbon is replaced by OH we obtain a monohydric alcohol; if two hydrogens attached to *different* carbon atoms are exchanged for hydroxyls we obtain a dihydric alcohol, and so on. Alcohols are known containing three, four, five, six and more hydroxyl groups.

Examples			
	$CH_3 \cdot OH$	$\underset{\Large CH_2}{\overset{OH}{\vert}}—\underset{\Large CH_2}{\overset{OH}{\vert}}$	$\underset{\Large CH_2}{\overset{OH}{\vert}}-\underset{\Large CH}{\overset{OH}{\vert}}-\underset{\Large CH_2}{\overset{OH}{\vert}}$
	Monohydric alcohol Methyl alcohol	Dihydric alcohol Ethylene glycol	Trihydric alcohol Glycerol

If two or more hydroxyl groups are attached to the same carbon atom, they represent an unstable formation. In such cases, with few exceptions, water is eliminated and oxygen remains united to carbon by a double bond, *e g*,



According as the hydroxyl group is linked to a primary, secondary or tertiary carbon atom (p. 99), we speak of a primary, secondary or tertiary alcohol.

Primary alcohols therefore contain the group $—CH_2 \cdot OH$. On oxidation[1] they are first converted into aldehydes, the group $—CH_2 \cdot OH$ being transformed into $—CH : O$. The latter on further oxidation form acids, containing the group $—COOH$ and having the same number of carbon atoms as the original alcohol.

Secondary alcohols contain the group $>CH \cdot OH$. These on oxidation are converted into ketones of the same number of carbon atoms, the group $>CH \cdot OH$ being oxidised to $>C : O$. On further oxidation the molecule breaks up, yielding acids containing a smaller number of carbon atoms.

Tertiary alcohols contain the group $\equiv C \cdot OH$. They break up on oxidation, giving ketones and acids, each containing fewer carbon atoms than the original alcohol.

$R \cdot CH_2 \cdot OH$	$\begin{matrix} R \\ R \end{matrix}\!\!>CH \cdot OH$	$\begin{matrix} R \\ R \\ R \end{matrix}\!\!\equiv C \cdot OH$
Primary alcohol	Secondary alcohol	Tertiary alcohol

Isomerism and nomenclature.—As in the case of hydrocarbons, we may have structural isomerism among alcohols due to differences in the linking of the carbon chains (I and II), the primary alcohol which

[1] For the mechanism of the process of oxidation see Wieland, *Ber.*, 1912, 45, 488, 2606; *Ber.*, 1913, 46, 3327.

corresponds to the normally constituted hydrocarbon being termed a normal alcohol

I CH_3 CH_2 CH_2 CH_2 OH

Normal primary butyl alcohol or propyl carbinol

II $\begin{matrix} H_3C \\ H_3C \end{matrix}\!\!>CH\ CH_2\ OH$

Isobutyl alcohol or isopropyl carbinol

III CH_3 CH_2 $CHOH$ CH_3

Normal secondary butyl alcohol or methyl ethyl carbinol

IV $\begin{matrix} H_3C \\ H_3C \\ H_3C \end{matrix}\!\!\!>C\ OH$

Tertiary butyl alcohol or trimethyl carbinol

Isomerism may also be occasioned by the different position of the hydroxyl in the molecule (I and III), or both these variations may occur together (I and IV)

A convenient nomenclature for such isomerides is obtained by considering them as substitution products of methyl alcohol, CH_3OH, by naming the latter carbinol and the higher alcohols as substituted carbinols (see above formulæ)

According to the Geneva nomenclature, the names of the alcohols are obtained from those of the hydrocarbons from which they are derived by replacing the final -e by -ol Polyhydric alcohols are designated as diols, triols and so on

CH_3 OH — Methyl alcohol, Methanol

HO CH_2 CH_2 OH — Glycol or ethandiol

HO CH_2 $CHOH$ CH_2 OH — Glycerol, propantriol

CH_2 CH CH_2OH — Allyl alcohol, 1 propene 3 ol

If a hydroxyl group is attached to a side chain, the name of the latter takes the termination -ol

MONOHYDRIC ALCOHOLS

As already mentioned, these may be derived from saturated or unsaturated hydrocarbons The unsaturated alcohols differ from the saturated in their additive properties only, resembling them in all typical reactions, so that they are conveniently treated together

The *physical properties* of the monohydric alcohols vary from member to member, just as is the case with any other homologous series The first members are mobile liquids—gaseous alcohols being unknown — after which follow those of oily consistency, and from dodecyl alcohol, $C_{12}H_{25}OH$, onwards they are wax-like solids Solubility in water diminishes with increase in molecular weight, the first members of the series being miscible in all proportions, whereas the higher alcohols are quite insoluble The lower compounds possess a characteristic alcoholic smell and taste, the intermediate members have an unpleasant smell, and those of high complexity are

tasteless and odourless For alcohols of similar structure the boiling-point rises regularly with increase of molecular weight Each difference of CH_2 corresponds to a rise of approximately 20° The highest members (above C_{16}) decompose on distillation, unless this is conducted under diminished pressure Primary alcohols boil higher than the isomeric secondary, and these again higher than the corresponding tertiary compounds The specific gravity is in all cases less than unity

It must be emphasised that the *chemical behaviour* of the hydrogen atom in the hydroxyl group OH, a group common to all alcohols, is very different from that of the hydrogen atoms in the alkyl radical, being directly replaceable by metals such as sodium and potassium, with evolution of hydrogen and formation of alcoholates

$$\underset{\text{Ethyl alcohol}}{C_2H_5\ OH} + Na = \underset{\text{Sodium ethoxide}}{C_2H_5\ ONa} + H$$

Alcohols react with acids to form *esters*, *e g* ethyl nitrate

$$\underset{\text{Ethyl alcohol}}{C_2H_5\ OH} + HNO_3 = \underset{\text{Ethyl nitrate}}{C_2H_5\ O\ NO_2} + H_2O$$

$$NaOH + HNO_3 = NaNO_3 + H_2O$$

As already indicated, we may compare esters to the salts of inorganic chemistry, and the formation of esters from alcohols to that of salts from bases Nevertheless these processes differ distinctly in their mechanism The formation of a salt is an ionic reaction and proceeds instantaneously, whereas ester formation from acid and unionised alcohol progresses slowly [1]

Alcohols also resemble the hydroxide bases in combining, with elimination of water, to produce anhydrides corresponding to the inorganic oxides These anhydrides are termed *ethers*

$$2C_2H_5OH - H_2O = \underset{\text{Diethyl ether}}{C_2H_5\ O\ C_2H_5} \qquad 2LiOH - H_2O = Li_2O$$

The dehydration of alcohols may also give rise to olefines (p 112), $C_2H_5OH \longrightarrow CH_2\ CH_2$ This occurs very readily in the case of tertiary alcohols

On treatment with phosphorus halides the hydroxyl group of the alcohols is replaced by halogen, with the formation of alkyl halides (p 119)

Methyl magnesium iodide interacts with alcohols, or in general any hydroxy compound, with liberation of one molecule of methane for each hydroxyl group present

$$CH_3\ MgI + R\ OH = CH_4 + R\ OMgI$$

The methane so formed is easily recognised and can be quantitatively

[1] The rate of esterification of alcohols varies with their constitution and diminishes progressively as we pass from primary to secondary and from the latter to tertiary alcohols *Cf* Menschutkin, *Ann*, 1879, 197, 193; Michael, *Ber*, 1909, 42, 3157

estimated This reaction may be used for determining the number of hydroxyl groups in a compound[1]

The characteristic behaviour on oxidation, which serves for the identification of primary, secondary and tertiary alcohols, has already been discussed above

Primary, secondary and tertiary alcohols differ also in their behaviour towards hot reduced copper, as was shown by Sabatier and Senderens[2] On being led over reduced copper at 300° primary alcohols break up into aldehydes and hydrogen, secondary alcohols yield ketones and hydrogen, and tertiary compounds decompose into water and olefines

$$\underset{\text{Ethyl alcohol}}{CH_3\cdot CH_2\cdot OH} = \underset{\text{Acetaldehyde}}{CH_3\cdot CH:O} + H_2$$

$$\underset{\text{2 Propanol}}{CH_3\cdot CHOH\cdot CH_3} = \underset{\text{Acetone}}{CH_3\cdot CO\cdot CH_3} + H_2$$

$$\underset{\text{2-Methyl 2 propanol}}{\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C(OH)\cdot CH_3} = \underset{\text{2 Methyl propene}}{\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!C:CH_2} + H_2O$$

With halogens the alcohols are not substituted but oxidised

Calcium chloride unites with alcohols to form double compounds which are decomposed by water, consequently it is not a suitable drying agent for alcohols

Methods of Formation—In order to convert a hydrocarbon into an alcohol it is necessary to proceed by way of the halogen compound, the halogen atom of which is then exchanged for a hydroxyl group by treatment with moist, freshly precipitated silver oxide, or by heating with lead oxide and water

$$C_2H_5I + AgOH = C_2H_5OH + AgI$$

Alcohols occurring in nature are found almost exclusively in combination with organic acids in the form of esters They may be prepared from these by heating with acids or alkalis, or by the action of superheated steam This process is termed *hydrolysis* (see p 147)

A method of great industrial importance is the formation of alcohols by the fermentation of carbohydrates (*e g* grape sugar)

$$\underset{\text{Grape sugar}}{C_6H_{12}O_6} = \underset{\text{Alcohol}}{2C_2H_5\cdot OH} + 2CO_2$$

By the action of nitrous acid on primary amines the group $-NH_2$ may be replaced by $-OH$, and a primary alcohol produced

$$C_2H_5\cdot NH_2 + HNO_2 = C_2H_5\cdot OH + N_2 + H_2O$$

[1] Zerewitinoff, *Ber*, 1907, 40, 2023 [2] Sabatier and Senderens, *C*, 1905, I, 1002 For many years the decomposition of alcohols by metallic oxides has been the subject of numerous investigations *Cf* Mailhe, *Ch Zeit*, 1909, 88, 18, 29 For a method of distinguishing between primary, secondary and tertiary alcohols with the aid of potassium hydroxide, see Guerbet, *C r*, 154, 222, 713

A general method of preparing primary alcohols consists in the reduction of aldehydes. In a similar manner ketones yield secondary alcohols.

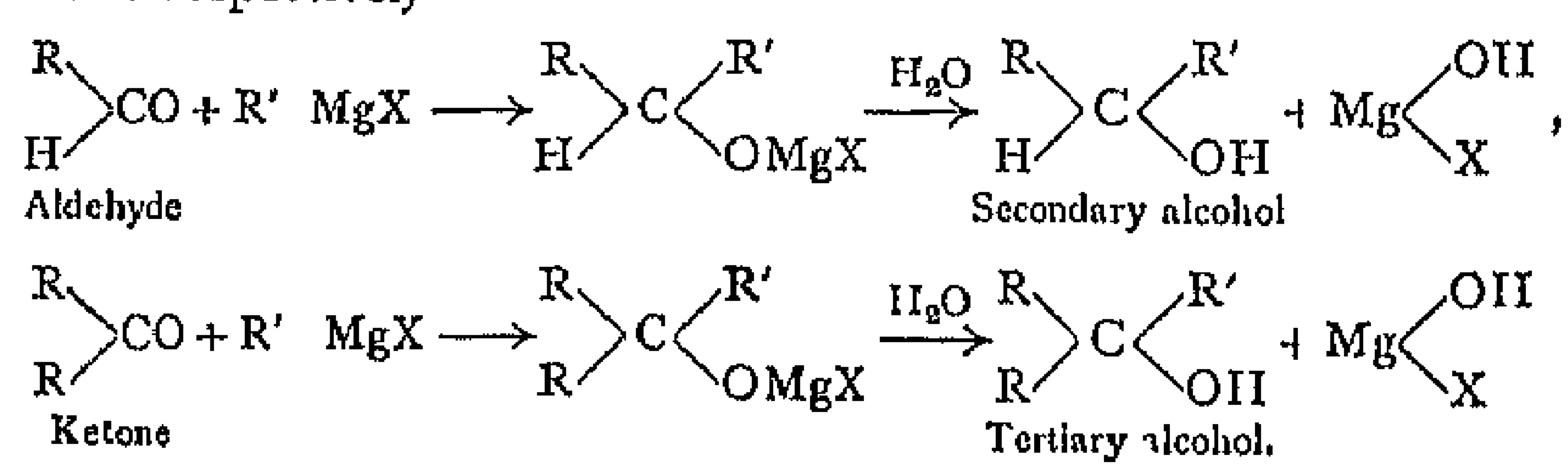
$$\underset{\text{Acetaldehyde}}{CH_3 \cdot CH : O} + 2H = \underset{\text{Ethyl alcohol}}{CH_3 \cdot CH_2 \cdot OH}$$

$$\underset{\text{Acetone}}{CH_3 \cdot CO \cdot CH_3} + H_2 = \underset{\text{Dimethyl carbinol}}{CH_3 \cdot CH(OH) \cdot CH_3}$$

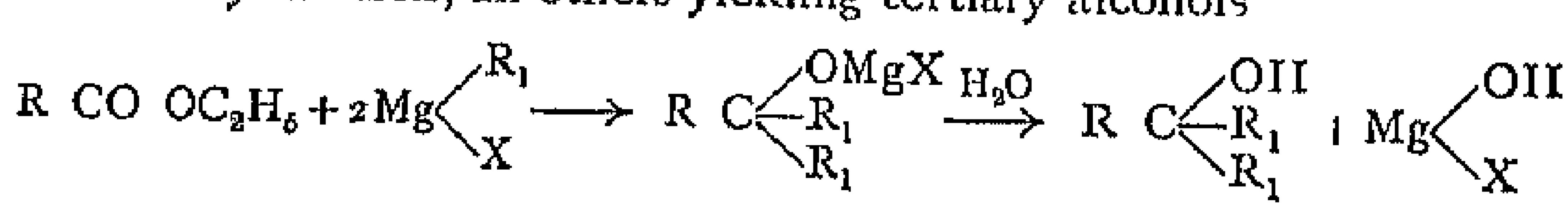
It is also practicable to bring about the phytochemical reduction of aldehydes and ketones by means of living yeast.[1] The biological character of the reaction is indicated in those cases where an asymmetric carbon atom is involved by the optical activity of the secondary alcohols formed.

Acid chlorides and acid anhydrides may also be reduced to alcohols by means of sodium amalgam or metallic sodium.

More recently numerous syntheses of alcohols have been effected with the aid of organo-magnesium halides. The latter unite with aldehydes and ketones forming addition products, which when decomposed with water and dilute acid yield secondary and tertiary alcohols respectively.[2]



Alcohols are also obtained by the action of organo-magnesium compounds on esters; the use of formic esters leads to the production of secondary alcohols, all others yielding tertiary alcohols.



The action of acid chlorides or anhydrides on organo-magnesium halides again results in the formation of tertiary alcohols.

If dry oxygen is led through an ethereal solution of an organo-magnesium compound at the ordinary temperature, the gas is absorbed according to the equation $R \cdot MgX + O = R \cdot O \cdot MgX$. On decomposing the product of reaction with water in the usual way, an alcohol is obtained.[3]

Tertiary alcohols are also formed together with ketones when carbon monoxide interacts with sodium alkyls.[4]

[1] Neuberg and Nord, *Ber.*, 1919, 52, 2237. [2] Grignard, *C. r.*, 1900, 130, 1322. Zelinsky, *Ber.*, 1902, 35, 2140. [3] *C. r.*, 1904, 138, 1048. Meldola, *J. S. C. I.*, 1910, 29, 737. [4] Schlubach, *Ber.*, 1919, 52, 1910.

Methyl alcohol, *methanol*, *carbinol* or *wood spirit*, CH_3OH, is found in the combined state in nature, e.g. in the form of methyl salicylate in oil of wintergreen, and as the methyl ester of anthranilic acid in oil of orange flowers.

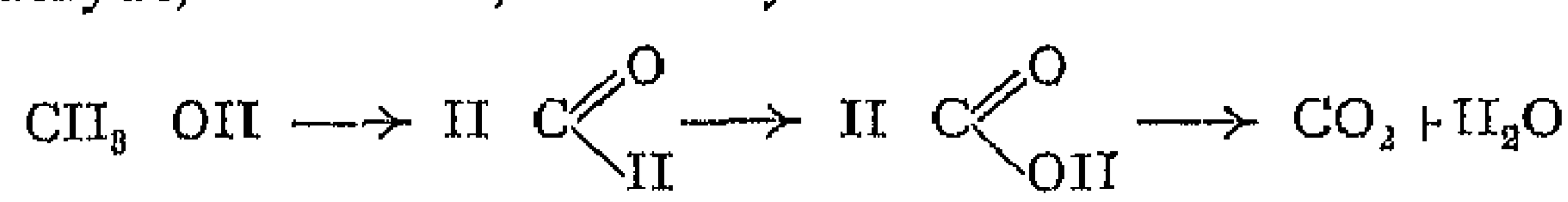
It has long been prepared technically by the dry distillation of wood in iron retorts at the lowest practicable temperature. Under these conditions a certain amount of gas is produced, together with a fluid distillate consisting of an aqueous liquid (pyroligneous acid) and wood tar. Wood charcoal remains behind in the retort. The aqueous layer separating from the tar contains a large proportion of water in addition to a number of other substances, chief among which are acetic acid, acetone and methyl alcohol. One hundred parts of wood yield a little more than one part of methyl alcohol. The acetic acid in the pyroligneous liquor is first neutralised by the addition of lime, after which the methyl alcohol, acetone and a number of other substances of less importance are isolated by fractional distillation. The methyl alcohol may be rendered anhydrous by boiling it for some time with freshly prepared lime and subsequently distilling several times over metallic calcium.[1]

Since 1923 methyl alcohol has been synthesised industrially from the carbon monoxide of water gas (*Patart* Process, Badische Anilin- und Soda Fabrik):

$$CO + 2H_2 = CH_3OH$$

The reduction is effected by means of hydrogen at high temperatures (450°) and pressures (200 atmos.) in the presence of catalysts (zinc oxide and chromium oxide?). By varying the catalyst, *synthol*, a mixture of homologues of methanol, is produced.

Pure methyl alcohol is an inflammable liquid of boiling-point 64.6°, which is miscible in all proportions with water. In chemical behaviour it strongly resembles ethyl alcohol. On oxidation it is converted into formaldehyde, formic acid, and finally carbon dioxide:



Formaldehyde Formic acid

Crude wood spirit is used technically for the denaturisation of alcohol (preparation of methylated spirits) and in the manufacture of aniline dye stuffs and varnishes.

Ethyl alcohol, *ethanol*, *spirits of wine*, $CH_3 \cdot CH_2 \cdot OH$, is found occasionally in nature, e.g., as the butyric ester in unripe fruit of *heracleum giganteum* and in diabetic urine.

Formation and Preparation.—It may be obtained synthetically by the general methods of formation given above for primary alcohols. For example, ethylene

[1] Metallic magnesium is also recommended for this purpose, N. Bjerrum and L. Zechmeister, *Ber.*, 1923, 56, 894.

unites with sulphuric acid to give ethyl hydrogen sulphate, which on hydrolysis with water yields ethyl alcohol

$$C_2H_5 \cdot SO_4H + H_2O = C_2H_5 \cdot OH + H_2SO_4$$

As ethylene may be prepared from acetylene, and the latter from carbon and hydrogen, this reaction provides a complete synthesis of alcohol [1]

Alcohol is obtained industrially by fermentation processes based on the decomposition of various sugars, particularly grape sugar or glucose, $C_6H_{12}O_6$, in the presence of living yeast cells [2]

$$\underset{\text{Glucose}}{C_6H_{12}O_6} = \underset{\text{Ethyl alcohol}}{2C_2H_5 \cdot OH} + 2CO_2$$

In addition to ethyl alcohol a number of by-products are formed [3] which vary with the nature of the sugar employed and the conditions of fermentation Prominent among these are the higher alcohols, especially amyl alcohol $C_5H_{11} \cdot OH$, succinic acid, acetaldehyde and glycerol Alcohol is obtained from the fermented liquid by distillation, and is brought on to the market under different names, according to the proportion of alcohol and the nature of the by-products present Whisky or brandy contains 30 to 60 per cent alcohol, and spirits and methylated spirits for domestic and industrial use 70 to 90 per cent Higher concentrations are generally known briefly as alcohol

The starting material for the manufacture of any one of these products is not glucose, but less expensive substances from which glucose may be generated and subsequently fermented

In all there are three sources of raw material available for the manufacture of alcohol or alcoholic beverages

1 Starchy substances such as potatoes, corn, barley, rice

2 Materials containing sugar, such as (*a*) fruit in which glucose is found (*e g* grapes, plums), (*b*) cane and beet sugar, or the molasses from their manufacture (p 308), and (*c*) substances containing lactose

3 Already fermented liquids, such as wine which is not otherwise saleable

The most representative case is that in which starchy material forms the starting-point, when the following separate processes are to be distinguished in the production of alcohol I Formation of a solution containing sugars from the starchy raw material II Decomposition of the sugars in this liquid by fermentation III

[1] Berthelot, *C*, 1899, I, 1018 [2] Neuberg and Kerb, *Ber*, 1919, 52, 1679, also Zerner, *Ber*, 1920, 53, 325, Ohle and Neuscheller, *Ber*, 1929, 62, 1651 [3] Buchner and Meisenheimer, *Ber*, 1904, 37, 417, 1905, 38, 620, 1906, 39, 3201, 1910, 43, 1773, 1912, 45, 1633 Connstein and Lüdecke, *Ber*, 1919, 52, 1385 It is of the greatest practical and theoretical value to trace the intermediate products formed in the conversion of a carbohydrate into ethyl alcohol The practical importance lies in the possibility of isolating the intermediate compounds or of diverting the course of the degradation process The discovery described later, that glycerol may be prepared technically by *carrying out the* fermentation in the presence of sulphites, affords a good illustration of the manner in which the action of ferments may be controlled

Distillation of alcoholic liquid from the fermented mash. IV. Final rectification of the distillate.

When the manufacture is based on one of the above raw products other than starch, the procedure is modified. In the fermentation of material containing sugar, process I. is dropped out and process II. becomes the starting-point. If we are concerned with the treatment of already fermented liquids, a beginning is made with process III.

In *Stage I.* starch is converted by means of certain so-called *enzymes* (see p. 138) into a sugar maltose, which, under the influence of other enzymes present in yeast, interacts with water to give glucose.[1]

$$\underset{\text{Maltose}}{C_{12}H_{22}O_{11}} + H_2O = \underset{\text{Glucose}}{2C_6H_{12}O_6}$$

The former change is usually brought about on the industrial scale by means of *diastase*,[2] a white odourless and tasteless powder, the composition of which has not yet been accurately determined. It is produced during the germination of corn, and is found also in saliva and the juices of the pancreas, where it plays an important part in the digestive processes.

In the production of sugar from starch, diastase is not employed in the pure state but is used together with the whole corn in the form of *malt*, which is preferably obtained by the germination of barley. The simplest method of preparation is to allow the moist barley to germinate in the dark at 15°, in layers about 12 cm. high.

The malt is next mixed with water and unmalted corn, when the latter is transformed into sugar and the liquid or mash so obtained is then ready for fermentation. In another process, potatoes are converted into a thin homogeneous paste by treatment with superheated steam, and malt subsequently added. At a temperature of 60° to 62° the formation of maltose is complete in twenty minutes.

Stage II.—The sugar in the "mash" obtained in this manner is then fermented by the addition of yeast, and the fermentation allowed to proceed at a temperature not higher than 33°.[3]

Fermentation of the mash occupies three to four days, and is accompanied by the evolution of carbon dioxide and consequent frothing of the liquid.

Very different views have been expressed as to the significance of the processes underlying alcoholic fermentation. Pasteur believed

[1] Since maltose is also a fermentable sugar, we may consider the two sugars maltose and glucose to be the immediate source of ethyl alcohol in the above process. [2] Starch may also be converted into sugar by heating with dilute sulphuric acid. [3] In addition to the alcoholic fermentation of saccharine liquids various other reactions are classed as fermentation processes. Milk sugar fermented with *bacterium lacticum* yields lactic acid, a reaction known as lactic fermentation and which causes the souring of milk in air (Buchner and Meisenheimer, *Ann.*, 1906, 349, 125). Under the influence of *Bacillus butyricus* this lactic acid may be transformed into butyric acid (Buchner and Meisenheimer, *Ber.*, 1908, 41, 1410). Succinic, citric, and other acids occurring in plants may also be obtained by fermentation.

fermentation to be a purely physiological action, inseparably bound up with the life of the yeast cells and actuated by cellular metabolism

Liebig, on the other hand, considered it to be a purely chemical change The point was settled later by E Buchner, who submitted a mixture of yeast and fine sand to strong pressure, disrupting the cell walls and obtaining an "expressed yeast juice" which no longer contained living cells, but nevertheless possessed strong fermentative power This ability to induce fermentation was retained even after the liquid had been evaporated *in vacuo* and the dry mass again brought into solution

The chemical changes taking place during fermentation are therefore due to the activity of this substance, named *zymase*, which belongs to the enzyme group The yeast cells only participate in the process of fermentation in so far as they generate zymase Alcoholic fermentation may therefore be defined as the change brought about by the action of zymase on certain sugars

Buchner has also shown that other fermentation processes, such as lactic acid fermentation, are not produced by the fungi themselves but are due to the action of enzymes contained in them [1]

Enzymes or unorganised ferments occur widely in plant and animal life and play an important part in metabolism, but little is known as to their chemical composition as few have even been obtained in the relatively pure state Up to the present it has only been possible to identify them by their chemical action Similarly, little can be said with certainty as to the mechanism of the reaction In all probability they do not undergo decomposition themselves but develop their fermentative activity solely by catalytic action It appears to be a characteristic property of the enzymes that each shows its activity towards one definite chemical compound alone Emil Fischer, to whose work we owe much of our knowledge of these substances, has compared the relationship between enzyme and compound attacked to that between a key and its lock This metaphor applies so completely that the enzyme does not even attack the stereoisomeride of the compound towards which it shows its activity The selectivity is probably connected with the asymmetry of the enzyme molecule

It was originally believed that enzymes had a number of points in common with proteins and were possibly derived from them Recent investigations by Willstätter [2] and others have now shown that enzymes may be further purified by fractional absorption of the active substance on (and fractional elution from) a variety of absorbent materials, *e g*, alumina, kaolin, tristearin, lead phosphate Preparations of lipase, invertase and peroxidase obtained in this way, although in a high state of activity, are free from all recognisable properties of protein Hence these at least are not related to proteins in structure Willstätter regards an enzyme as a composite system, comprising a specific catalytic molecule or group associated with a non-specific catalytically inactive colloidal product

In the fermentation of saccharine fluids by living yeast certain other chemical changes take place, which may be ascribed to the life processes of the yeast itself For this reason the simple chemical

[1] See Note 3 on previous page [2] Willstätter, *J C S*, 1927, 1359

equation, according to which 100 parts of a sugar, $C_6H_{12}O_6$, should yield 51 11 parts of alcohol and 49 33 parts of carbon dioxide, is not strictly in accordance with the actual facts Yeast uses up sugar in maintaining its life, and even with fermentation experiments on the small scale, in which all precautions are taken, there are obtained from 100 gms pure sugar, $C_6H_{12}O_6$, no more than 48 49 gms alcohol

A theory of alcoholic fermentation advanced by Neuberg[1] supposes the process to occur through the intermediate formation of pyruvic acid Under the influence of a ferment, carboxylase, present in yeast and its preparations (*e g*, expressed yeast juice), pyruvic acid readily decomposes into carbon dioxide and acetaldehyde, and it is supposed that the latter undergoes phytochemical reduction to alcohol Both of these compounds can be isolated in quantity from a yeast fermentation, pyruvic acid by the addition of calcium carbonate[2] and acetaldehyde by fermenting in the presence of sodium sulphite, which serves to "fix" the aldehyde as it is formed

Stage III—From the fermented mash, in which the concentration of alcohol does not exceed 18 per cent, alcohol is removed by distillation For this purpose stills are employed which permit the direct distillation of approximately 90 per cent alcohol The aqueous mass which remains behind in the distillation vessel is termed "spent wash," and is utilised as cattle food, in it are to be found nearly all the proteins contained in the starting material

Stage IV—The raw spirit is next refined by rectification, at least four separate fractions being collected as follows —

1 First runnings, *i e*, low-boiling by-products consisting mainly of acetaldehyde, boiling-point 20 8°

2 Spirit of 93 per cent ethyl alcohol

3 Spirit of 90 per cent ethyl alcohol

4 Final runnings, *i e*, higher boiling products, containing amongst other compounds fermentation amyl alcohol (*fusel oil*), which consists of a mixture of isomeric alcohols of the formula $C_5H_{11}OH$

For the preparation of alcohol of higher purity than 93 per cent, fractions 2 and 3 are again submitted to fractional distillation, whereby alcohol containing 96 per cent by volume is obtained

Between operations III and IV, that is after the preparation of raw spirit and before refining, the liquid is sometimes filtered through charcoal to remove fusel oil

Finally, if completely anhydrous alcohol is required, the rectified spirits (with 95 to 96 per cent alcohol) is distilled over quicklime ignited potash, anhydrous copper sulphate or barium oxide, in order to remove the bulk of the water Last traces of water may be removed

[1] C Neuberg, "Die G'lrungsvorgänge und der Zuckerumsatz der Zelle," Jena, 1913 See also *Biochem Z*, 1918, 92, 234, *Ber*, 1919, 52, 1677 [2] Fernbach (*J Inst Brewing*, 1916, 22, 354) has shown that large quantities of pyruvic acid are formed during alcoholic fermentation

by treatment with the requisite amount of sodium and subsequent distillation.

Attention has recently been drawn to the use of other raw material for the production of alcohol, such as wood, wood shavings and the sulphite liquor from the manufacture of cellulose. The latter is rich in the carbohydrate constituents of plant cells, particularly sugar, and after neutralisation may be fermented by a special kind of yeast to yield alcohol. Wood and wood shavings,[1] after hydrolysis by heating under pressure with dilute acids, yield 25 to 80 per cent. of soluble carbohydrate, of which 80 per cent. may be obtained as fermentable sugar. Another possible source of alcohol is in calcium carbide or acetylene. Under the catalytic influence of mercury salts, acetylene in warm acid solution combines with the elements of water to give acetaldehyde, which may then either be reduced to alcohol or oxidised to acetic acid[2] (p. 118).

Properties.—Ethyl alcohol is a colourless mobile liquid with a pleasant, pungent smell. It boils at 78.3° and melts at −111.8°, sp. gr. 0.789 at 20°. Alcohol burns with a pale blue non-luminous flame. It is extremely hygroscopic and mixes in all proportions with water, when a contraction in volume takes place. The greatest diminution occurs when 53.9 vols. alcohol are added to 49.8 vols. water, the mixture occupying 100 vols. instead of 103.7. The concentration of aqueous solutions of alcohol may be ascertained by determining the specific gravity by the use of suitable hydrometers. In technical work the concentration is usually quoted in percentage by volume, and in scientific work in percentage by weight. Alcohol is an excellent solvent for many organic compounds such as resins and oils. It is readily oxidised, being converted first into aldehyde and then into acetic acid.

Uses.—In addition to extensive use as a beverage, alcohol is employed for a variety of industrial and scientific purposes. Owing to its value as a solvent for resins and dye-stuffs it is required in quantity for the preparation of colourless and coloured varnishes. It enters into the production of a number of coal-tar dyes, alkaloids and other preparations such as perfumes and collodion. As the starting material it functions in the preparation of numerous organic compounds such as ether, chloroform, chloral and fulminates of mercury and silver. In scientific laboratories it is one of the commonest solvents and is also used as a source of heat.

Alcohol intended for use as a beverage is usually heavily taxed and therefore expensive. On the other hand, alcohol for industrial purposes is now duty free in most countries, including Great Britain, where for many years the tax very seriously affected the industry in

[1] Tomlinson, *Chem. Trade Journ.*, 1918, 68, 103; *C.*, 1919, IV, 543. [2] Grünstein, *Z. ang. Ch.*, 1919, 82, 335.

fine chemicals Industrial alcohol, however, must first be denatured or rendered unfit for human consumption by the addition of certain substances The denaturants may be crude wood spirit and pyridine bases, as in Germany, a mixture of wood naphtha, mineral naphtha and pyridine as in Great Britain, or benzine and wood spirit as in America In addition, incompletely denatured alcohol (industrial methylated spirits), or alcohol containing special denaturants, is allowed for use in those industries where ordinary methylated spirits would be unsuitable

Detection of Ethyl Alcohol—On warming alcohol with iodine and potassium hydroxide, iodoform is produced (p 124) This reaction is very sensitive, and by its use the presence of 1 part of alcohol in 2000 parts of water may be detected Several other compounds, however, including acetone, also give this test

Sodium ethoxide, *sodium ethylate*, C_2H_5ONa, is obtained by dissolving sodium in excess of absolute alcohol

$$2C_2H_5 \cdot OH + 2Na = 2C_2H_5 \cdot ONa + H_2$$

It is readily soluble in alcohol, giving a solution which turns brown in air owing to oxidation The pure compound forms a white powder and is frequently employed alone or in alcoholic solution as a condensing agent in organic synthesis

Tribromoethyl alcohol, "*Avertin*," $CBr_3 \cdot CH_2 \cdot OH$, is a white crystalline substance, m p 79 to 80°, which is used medicinally for inducing rectal narcosis

Propyl alcohols, *propanols*, $C_3H_7 \cdot OH$ Both of the theoretically possible structural isomerides of this formula are known, viz —

$$H_3C \cdot CH_2 \cdot CH_2 \cdot OH \quad \text{and} \quad H_3C \cdot CH(OH) \cdot CH_3$$

Normal propyl alcohol, 1-Propanol, Ethyl carbinol	Isopropyl alcohol, 2 Propanol, Dimethyl carbinol

The constitution of both compounds follows from their behaviour on oxidation (see p 130) Normal propyl alcohol on treatment with chromic acid is converted successively into propionaldehyde and propionic acid, showing it to be a primary alcohol, isopropyl alcohol, on the other hand, yields acetone and is therefore a secondary alcohol

Normal propyl alcohol, boiling-point 97°, sp gr 0 8044 at 20°, occurs in fusel oil, from which it is obtained by fractional distillation In taste and smell it resembles ethyl alcohol

Isopropyl alcohol, boiling point 83°, sp gr 0 7887 at 20°, is best prepared from glycerol through the intermediate formation of isopropyl iodide, $CH_3 \cdot CHI \cdot CH_3$ It is also formed by the reduction of acetone with sodium amalgam, a further proof of the constitution given above

Butyl alcohols, $C_4H_9 \cdot OH$ Four structural isomerides are theoretically possible, all of which are known

1 **Normal butyl alcohol,** *propyl carbinol*, *1 butanol*, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2OH$, is prepared by reducing butyric aldehyde or by the fermentation of glycerol It is a colourless liquid, b p 116 8°, with a smell of both alcohol and fusel oil On oxidation it yields butyric aldehyde and normal butyric acid, thus confirming the above formula, which may also be deduced from its method of synthesis

2 **Secondary butyl alcohol,** *methyl ethyl carbinol*, *2 butanol*, $CH_3 \cdot CH_2 \cdot CH(OH) \cdot CH_3$, may be obtained from methyl ethyl ketone by reducing it in moist ethereal solution with metallic sodium, or from the iodide $CH_3 \cdot CH_2 \cdot CHI \cdot CH_3$ by the method indicated on p 133 This iodide can be prepared from the alcohol erythritol, $C_4H_{10}O_4$, by the action of hydriodic acid Secondary butyl alcohol is a colourless pleasant smelling liquid boiling at 98° On oxidation it yields methyl ethyl ketone, which on further oxidation yields acetic acid

Optically active *sec* butyl alcohols may be prepared by the method of Pickard and Kenyon The racemic alcohol is combined with phthalic anhydride to give butyl hydrogen phthalate, and this is then resolved by recrystallising the brucine salt The active acid esters so obtained yield the active alcohols[1] on hydrolysis

3 **Isobutyl alcohol,** *fermentation butyl alcohol*, *isopropylcarbinol*, *2-methyl-3-propanol*, $(CH_3)_2CH \cdot CH_2OH$, is formed in small amount during the alcoholic fermentation of sugar. It boils at 107° and is therefore found in fusel oil, particularly in that obtained from potato spirit From this source it may be isolated by rectification in suitably designed columns It is soluble to some extent in water, and in smell resembles both alcohol and fusel oil On oxidation it first yields isobutyric aldehyde and then isobutyric acid

Amyl alcohols, $C_5H_{11}OH$, should exist according to theory in eight isomers, four of which are primary, three secondary and one tertiary in structure All of these are known

1 $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2(OH)$, normal amyl alcohol, b p 137°
2 $(CH_3)_2CH \cdot CH_2 \cdot CH_2(OH)$, fermentation amyl alcohol, b p 131°
3 $\begin{array}{l} CH_3 \cdot CH \cdot CH_2(OH) \\ \quad\quad\; | \\ \quad\quad CH_2 \cdot CH_3 \end{array}$, usually known as active amyl alcohol, b p 125°
4 $(CH_3)_3C \cdot CH_2(OH)$, tertiary butyl carbinol, b p 112°
5 $(C_2H_5)_2CH(OH)$, diethyl carbinol, b p 117°
6 $\begin{array}{l} CH_3 \cdot CH_2 \cdot CH_2 \\ \qquad\qquad CH_3 \end{array} \!>\! CH(OH)$, methyl *n* propyl carbinol, b p 119°
7 $\begin{array}{l} (CH_3)_2CH \\ \qquad CH_3 \end{array} \!>\! CH(OH)$, methyl-isopropyl-carbinol, b p 112°
8, $\begin{array}{l} CH_3CH_2 \\ (CH_3)_2 \end{array} \!>\! C(OH)$, dimethyl-ethyl-carbinol, b p 102 5°

Only those alcohols which possess special interest will be discussed here

Fermentation amyl alcohol, isoamyl alcohol, $(CH_3)_2CH \cdot CH_2 \cdot CH_2OH$, b p 131°, is the chief constituent of fusel oil The name is derived from starch (*amylum*), these alcohols having been first isolated as by-products in the fermentation of starch to ethyl alcohol According to Ehrlich,[2] the production of fusel oil during fermentation is a result of the protein-forming activity of the living yeast cells and is due to the

[1] Pickard and Kenyon, *J C S*, 1913, **103**, 1938 [2] F Ehrlich, *Ber*, 1907, **40**, 1027.

disruption of certain amino acids, particularly leucine, isoleucine and valine, by the yeast to satisfy its need for nitrogen and for the production of zymase. The corresponding higher alcohols are left behind as non-assimilable products of metabolism. In this way *l*-leucine gives rise to inactive isoamyl alcohol, *l*-isoleucine to laevorotatory amyl alcohol, and valine to isobutyl alcohol. It is probable that the other alcohols which occur to a smaller extent in fusel oil are also derived from amino acids.

$$\underset{l\text{-Leucine}}{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\cdot CH_2\cdot CH(NH_2)\cdot CO_2H} + H_2O = \underset{\text{Inactive isoamyl alcohol}}{\begin{matrix}CH_3\\CH_3\end{matrix}\!\!>\!CH\cdot CH_2\cdot CH_2OH} + CO_2 + NH_3$$

The earlier view that amyl alcohol was produced during fermentation by the action of bacteria on sugar has therefore proved incorrect. The chief sources of fusel oil are the amino acids already present as such in the natural mash and those produced from proteins of the raw material during the conversion of the malt into sugar. The proteins contained in the yeast play very little part in the formation of fusel oil.

A practical outcome of the above is that the content of fusel oil in raw spirit may be increased by the addition of leucines and their homologues to the fermenting mash. On the other hand, by the addition of sufficient amounts of other nitrogenous compounds which are easily assimilable by the yeast, the formation of higher alcohols during fermentation may be almost completely avoided. Amyl alcohol is a valuable article of commerce owing to its numerous technical applications, *e.g.*, as a solvent in the manufacture of varnish, and in the form of amyl acetate and other esters in the confectionery, mineral water and fruit essence industries.

Fermentation amyl alcohol is always accompanied by **laevorotatory amyl alcohol**, 2-methyl-1-butanol, $CH_3\cdot CH_2\cdot CH(CH_3)\cdot CH_2OH$, which is of interest as one of the simplest examples of an optically active compound. The proportion of optically active alcohol in the commercial alcohol is very variable. The problem of separating these two products, the output of which amounts to thousands of tons per annum, was solved by Marckwald.[1] An examination of the fusel oils isolated from the spirit prepared from potatoes, corn and beet sugar molasses respectively, with reference to the relative amounts of amyl alcohols present, showed that a productive source of active amyl alcohol was to be found in the fusel oil from molasses. The proportion of active alcohol in the latter varies between 48 and 58 per cent. One of the methods of separation worked out by Marckwald was based on earlier experiments of Pasteur, the two alcohols being converted first into the amyl sulphuric acids, the mixed barium salts of which may be separated by fractional crystallisation and the pure alcohols regenerated from the individual salts. Although the two salts form an unbroken series of

[1] *Ber.*, 1901, **34**, 479, 485; 1902, **35**, 1595; 1904, **37**, 1038; 1909, **42**, 1583.

mixed crystals, their separation may be effected completely and comparatively easily by careful fractional crystallisation

The separation of the amyl alcohols of fusel oil may also be effected by conversion into the solid esters of 3-nitrophthalic acid and subsequent fractional crystallisation

The optical activity of pure *d*-amyl alcohol[1] (2-methyl-1-butanol) is $[\alpha]_D - 5.83°$

Dimethyl ethyl carbinol, *tertiary amyl alcohol*, *amylene hydrate*, $(CH_3)_2C(OH) C_2H_5$, is a liquid with a smell like camphor It is used as a hypnotic and is prepared industrially from fermentation amyl alcohol When the latter is distilled with zinc chloride, water is split off and a mixture of isomeric amylenes of the formula C_5H_{10} obtained On being shaken with aqueous sulphuric acid at $-20°$ this is partly dissolved, giving a solution of the acid sulphate of *tert* amyl alcohol, which on subsequent dilution and distillation yields the alcohol itself. *Trimethyl-ethylene* (b p 37°), an amylene of the formula $(CH_3)_2C\ CH\ CH_3$, is prepared by heating the alcohol to 200° and is used as a narcotic under the name of *pental*

Among the higher alcohols only cetyl alcohol and myricyl alcohol need be mentioned

Cetyl alcohol, *hexadecyl alcohol*, $C_{16}H_{33}OH$, occurs as the palmitic ester in spermaceti, from which it is obtained by hydrolysis with alcoholic potash It is a white crystalline mass of melting point 49 5°

Myricyl or melissyl alcohol, $C_{30}H_{61}OH$, is found as the palmitic ester in bees wax and melts at 85°

UNSATURATED MONOHYDRIC ALCOHOLS

These may be derived from the olefines or acetylenes, and consequently show on the one hand the behaviour typical of the saturated alcohols, and on the other the additive properties of the unsaturated hydrocarbons

It should be remembered that the grouping C CH OH is unstable and readily passes over into the group CH—CH O (see p 62), *i e*, the alcohols in which the hydroxyl group is attached to a doubly bound carbon atom are for the most part unstable and isomerise into the corresponding aldehydes An example of this type is *vinyl alcohol*, ethenol, CH_2 CH OH, traces of which are supposed to be present in commercial ether All reactions which might be expected to give this compound yield instead its isomeride acetaldehyde, CH_3 CH O

On the other hand, unsaturated alcohols in which the hydroxyl group is united to a singly bound carbon atom are stable and are known in large number. One of the most important of these is **allyl**

[1] Although laevorotatory, the alcohol is generally termed *d* amyl alcohol as most of its derivatives have a dextro rotation For derivatives of amyl alcohol compare O Aschan, *C*, 1918, II, 939

alcohol, 3-propenol, $CH_2=CH—CH_2OH$, which occurs in raw wood spirit (0·1 to 0·2 per cent). It may be prepared from allyl iodide by heating with water to 100°, or more conveniently from glycerol by heating to 260° with oxalic acid. As has been shown by Chattaway, this reaction involves the formation of a neutral glyceryl oxalate and its decomposition by heat into CO_2 and allyl alcohol. When oxidised

$$\begin{array}{l} CH_2OH \\ | \\ CHOH \\ | \\ CH_2OH \end{array} + \begin{array}{l} \\ \\ HOOC \\ \;\;\;\;| \\ HOOC \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CHO\;\;OC \\ |\;\;\;\;\;\;\;\;\;| \\ CH_2O\;\;OC \end{array} \longrightarrow \begin{array}{l} CH_2OH \\ | \\ CH \\ \| \\ CH_2 \end{array} + 2CO_2$$

under certain conditions it yields first acrylic aldehyde or acrolein and then acrylic acid, showing it to be a primary alcohol:

$$\underset{\text{Allyl alcohol}}{H_2C:CH\cdot CH_2OH} \longrightarrow \underset{\text{Acrolein}}{H_2C:CH\cdot CH:O} \longrightarrow \underset{\text{Acrylic acid}}{H_2C:CH\cdot COOH}$$

On oxidation with potassium permanganate, two hydroxyl groups are added to the allyl alcohol molecule, transforming it into glycerol:

$$\underset{\text{Allyl alcohol}}{H_2C:CH\cdot CH_2OH} \xrightarrow{H_2O+O} \underset{\text{Glycerol}}{CH_2OH\cdot CHOH\cdot CH_2OH}$$

Allyl alcohol is a pungent-smelling liquid, b.p. 96°; at −50° it solidifies to a mass of crystals. It unites with hydrogen and halogens, and forms an ozonide with ozone.[1] The latter is an unstable syrup which decomposes at room temperature, and on boiling with water is hydrolysed to yield an aldehyde (see p. 111).

A number of unsaturated alcohols and their corresponding aldehydes are found in the essential oils of plants associated with cyclic terpenes (p. 464), to which they are closely related in structure. Hence they are known as *olefinic* or *open chain terpene alcohols*. Well known examples of this class are *geraniol*, *nerol* and *citronellol*.

Geraniol, $(CH_3)_2C:CH\cdot CH_2\cdot CH_2\cdot C(CH_3):CH\cdot CH_2OH$, is a pleasant-smelling liquid, b.p. 121°/17 mm. It may be isolated from geranium oil or prepared by the reduction of the aldehyde citral, into which it is again transformed on oxidation. As will be seen later, it yields the cyclic terpene derivative *terpin*, p. 469, on treatment with dilute sulphuric acid.

Geraniol is the chief constituent of geranium oil, rose oil and lemon grass oil. **Nerol** appears to be a geometrical isomeride of geraniol. It has an odour of roses and is a valuable constituent of perfumes. **Citronellol**,

$${CH_3 \atop CH_2}\!\!>\!C\cdot CH_2\cdot CH_2\cdot CH_2\cdot \overset{\displaystyle CH_3}{\overset{|}{C}H}\cdot CH_2\cdot CH_2OH,$$

b.p. 117 to 118°/17 mm., occurs in the *l* form in rose oil and in the *d* form in citronella oil. As in many other compounds of this type, the terminal group ${CH_3 \atop CH_2}\!\!>\!C$ readily isomerises into ${CH_3 \atop CH_3}\!\!>\!C$ under the influence of reagents.

[1] Harries and Langheld, *Ann.*, 1905, **343**, 311.

Phytol, $C_{20}H_{39}OH$, is one of the higher unsaturated alcohols It possesses special interest as standing in close relationship to chlorophyll (the green colouring matter of leaves), from which it has been isolated by Willstatter[1] When chlorophyll is treated in cold alcoholic solution with oxalic acid, the atom of magnesium which is an integral part of the complex molecule is replaced by two atoms of hydrogen, and a wax-like substance called *phaeophytin* produced The latter is an ester, and on hydrolysis with cold alcoholic potash gives the alcohol phytol, $C_{20}H_{39}OH$ Phytol is an important constituent of the chlorophyll molecule, since it is obtained in approximately equal yield from the chlorophyll of all classes of plants It is a colourless oil, which cannot be distilled without decomposition except at extremely low pressures It boils at 145° under 0 03 mm pressure, and probably has the following structure[2]

$$\begin{array}{llllllll} CH_3 & CH & (CH_2)_3 & CH & (CH_2)_3 & CH & (CH_2)_3 & C\ \ CH\ \ CH_2OH \\ & | & & | & & | & & | \\ & CH_3 & & CH_3 & & CH_3 & & CH_3 \end{array}$$

Propargyl alcohol, 3 propinol, CH C CH_2OH, is an example of an alcohol derived from a hydrocarbon of the acetylene series It is obtained from mono bromoallyl alcohol by removing hydrogen bromide with potash It is a pleasant-smelling liquid of boiling point 114°, which directly adds on four atoms of bromine, and like the acetylene hydrocarbons yields explosive metallic compounds with ammoniacal solutions of cuprous chloride or silver nitrate

V

Esters of Monohydric Alcohols with Inorganic Acids

As already mentioned on p. 132, esters may be compared to metallic salts, and are produced by the union of acids and alcohols with simultaneous liberation of water Corresponding to halide salts are the esters of halogen acids, already treated on p 119 under the heading of monohalogen substitution products of the hydrocarbons Esters are also known of other mineral acids Polybasic acids give rise to several series of esters in the same manner as they form several series of salts

When the total replaceable hydrogen of an acid is displaced by alkyl groups, neutral esters are formed, corresponding to neutral salts These esters are mostly liquids of neutral reaction, often of very pleasant odour and almost or completely insoluble in water

If on the other hand the replaceable hydrogen of a polybasic acid is incompletely substituted by alkyl groups, an acid ester or ester acid is produced Acid esters are genuine acids and capable of exchanging

[1] Willstatter and Hocheder, *Ann*, 1907, 354, 205 [2] F G Fischer, *Ann*, 1928, 464, 69

the as yet unreplaced hydrogen for metals in the usual manner They are considerably less stable than the normal esters, are odourless and generally dissolve readily in water

$$\underset{\text{Ethyl hydrogen sulphate}}{C_2H_5HSO_4} \qquad \underset{\text{Diethyl sulphate}}{(C_2H_5)_2SO_4}$$

All esters are *hydrolysed* on heating with sodium or potassium hydroxide, or by treatment with superheated steam, when they break up into the alcohol and acid from which they are derived The former process has long been employed in the manufacture of soaps from fats and is therefore known as **saponification** Acid esters are often hydrolysed to the free acid and alcohol merely on being mixed with water at the ordinary temperature, but the action occurs more readily on boiling

$$C_2H_5NO_3 + KOH = C_2H_5 \cdot OH + KNO_3$$
$$C_2H_5HSO_4 + H_2O = C_2H_5 \cdot OH + H_2SO_4$$

Methods of Formation—1 Frequently by direct interaction of acid and alcohol

$$CH_3 \cdot OH + HCl = CH_3Cl + H_2O$$

Under these conditions polybasic acids first give rise to the acid esters

In this case there is no quantitative conversion of alcohol and acid into ester, but the formation of the latter ceases at a certain point which is called the equilibrium point This state of affairs is brought about by the hydrolytic action of the water liberated, and leads eventually to a state of equilibrium By employing an excess of acid or by removing the ester from the reaction mixture (*e g*, by continuous distillation) a larger yield may be attained

2 By the action of silver salts of the acids on alkyl halides[1]

$$C_2H_5I + AgNO_3 = C_2H_5NO_3 + AgI$$

3 By double decomposition between acid chlorides and alcohols or preferably sodium alcoholates

$$SO_2Cl_2 + 2C_2H_5OH = SO_2(OC_2H_5)_2 + 2HCl$$

Among the numerous esters of mineral acids the most interesting are those of sulphuric acid

Esters of Sulphuric Acid

Acid esters of sulphuric acid, $RHSO_4$, usually termed alkyl hydrogen sulphates, are produced on mixing alcohols with concentrated sulphuric acid or by the union of ethylene hydrocarbons with concentrated sulphuric acid (p 110)

$$SO_2(OH)_2 + C_2H_5 \cdot OH = SO_2\begin{cases} OC_2H_5 \\ OH \end{cases} + H_2O$$

They possess a strong acid reaction, and their salts are, for the most part, readily soluble in water Among the latter the alkali salts

[1] Sometimes an isomeride of the expected ester is obtained by this method.

crystallise well, and are used in a variety of reactions. Ethyl bromide is conveniently prepared by the dry distillation of a mixture of potassium ethyl sulphate and potassium bromide

$$KO \cdot SO_2 \cdot OC_2H_5 + KBr = KO \cdot SO_2 \cdot OK + C_2H_5Br$$

The alkali salts give mercaptans when heated with potassium hydrosulphide, thio-ethers with potassium sulphide, and alkyl cyanides with potassium cyanide.

Neutral esters of sulphuric acid, R_2SO_4, are produced by the action of heat on alkyl sulphuric acids, by heating alcohols with sulphuric acid, or alkyl iodides with silver sulphate. The most important neutral ester is **dimethyl sulphate**, which although employed for many years in industry as a methylating agent has only recently come into general use in the laboratory.[1] It is best prepared by the decomposition of methyl hydrogen sulphate at a high temperature

$$\underset{\text{Methyl hydrogen sulphate}}{SO_2\begin{cases}OCH_3\\OH\end{cases} + SO_2\begin{cases}OH\\OCH_3\end{cases}} = \underset{\text{Dimethyl sulphate}}{SO_2\begin{cases}OCH_3\\OCH_3\end{cases}} + SO_2\begin{cases}OH\\OH\end{cases}$$

Methyl hydrogen sulphate is obtained by treating methyl alcohol with chlorosulphonic acid or fuming sulphuric acid.

Dimethyl sulphate boils at 188°, strongly attacks the mucous membranes and is poisonous. It is a valuable methylating agent and may be substituted in all cases for methyl iodide, although under the usual experimental conditions only one of the two methyl groups is utilised. In general it reacts with much greater rapidity and gives better yields than methyl iodide. It is especially effective for the methylation of phenols.

When an alkaline solution of phenol is shaken for a short time with a molecular proportion of dimethyl sulphate, the phenol is practically quantitatively methylated.

$$\underset{\text{Sodium phenate}}{C_6H_5ONa} + (CH_3)_2SO_4 = \underset{\text{Anisole}}{C_6H_5OCH_3} + NaCH_3SO_4$$

Esters of nitric acid are produced by the action of alcohols on concentrated nitric acid, free from oxides of nitrogen. They are mobile liquids which are practically insoluble in water, and explode when rapidly heated.

The **esters of nitrous acid**, $R \cdot O \cdot NO$, are isomeric with the nitroparaffins, $R \cdot NO_2$, and of these only the isoamyl ester, $C_5H_{11} \cdot O \cdot NO$, usually known as amyl nitrite, need be mentioned. It is prepared by leading nitrogen trioxide into hot amyl alcohol, and is a yellow liquid of boiling-point 98°. It is employed in medicine (*amyl nitris*) on account of its property of expanding the blood vessels and relaxing the contractile muscles. It is also used in the preparation of nitroso- and diazo-compounds.

[1] F. Ullmann, *Ber.*, 1900, 33, 2476; *Ann.*, 1903, 327, 104; Graebe, *Ann.*, 1905, 340, 244. For the methylation of sugars see W. N. Haworth, *J. C. S.*, 1915, 107, 8.

Among less common inorganic esters, those of phosphoric acid[1] may prove to be of considerable value in the investigation of naturally occurring phosphorus compounds of physiological importance (see nucleic acids)

VI

Ethers

Ethers may be considered to be anhydrides of the alcohols in the same way as metallic oxides are anhydrides of the corresponding hydroxides According to whether the alkyl radicals united to the oxygen atom are similar or dissimilar, the compounds are known as simple or mixed ethers

$C_2H_5 \cdot O \cdot C_2H_5$	$C_2H_5 \cdot O \cdot CH_3$
Diethyl ether (Simple ether)	Methyl ethyl ether (Mixed ether)

They may be prepared

1 By the interaction of sodium alcoholates with alkyl halides in alcoholic solution

$$C_2H_5 \cdot O \cdot Na + I \cdot CH_3 = C_2H_5 \cdot O \cdot CH_3 + NaI$$

By this synthesis the structure of the ethers was first established by Williamson

2 By the action of sulphuric acid on alcohols This method of formation, which is described in detail below, is of great practical importance

3 Sabatier and Mailhe[2] have developed a general method for preparing esters and ethers, depending on the catalytic action of certain metallic oxides In this reaction an unstable alcoholate of the metal is produced as an intermediate product If the vapour of ethyl alcohol is led over precipitated alumina at temperatures between 240° and 260°, the dehydration of the alcohol does not result in the formation of ethylene, $C_2H_5OH = H_2O + C_2H_4$, but extends over two molecules of alcohol to give ether, $2C_2H_5OH = H_2O + (C_2H_5)_2O$ Methyl ether, $CH_3 \cdot O \cdot CH_3$, is obtained even more readily under these conditions, since the formation of an ethylene hydrocarbon is not possible in this case The unstable alcoholate $(CH_3O)_6Al_2$ is transformed immediately into $Al_2O_3 + 3(CH_3)_2O$ Titanium oxide, TiO_2, thorium oxide, ThO_2, and the blue oxide of tungsten, W_2O_5, may also be used as catalysts

The above is an example of the simple and convenient syntheses which have recently been effected with the aid of metallic oxides as catalysts In a similar manner it is possible to synthesise ethylene

[1] K Langheld, *Ber*, 1911, **44**, 2076 G Embden, *Z physiol Ch*, 1927, **167**, 114 [2] See also Mailhe and de Godon, *Bull Soc*, 1920 [iv.], **27**, 121.

hydrocarbons, aldehydes, ketones, thio alcohols and primary and secondary amines

4. By double decomposition between alkyl halides and silver oxide

$$2C_2H_5I + Ag_2O = (C_2H_5)_2O + 2AgI$$

Ethers are very mobile liquids of neutral reaction and are only sparingly soluble in water. They are comparatively inactive in a chemical sense and are quite stable towards acids and alkalis.

Ether, ethyl ether, $(C_2H_5)_2O$, is by far the best known and most important compound of this series. It is prepared technically and in the laboratory[1] by heating a mixture of nine parts of concentrated sulphuric acid and five parts of 90 per cent alcohol to a temperature of 135° to 140°. Ether and water distil over, and a continuous supply of alcohol is allowed to flow into the distillation vessel, where it is immediately acted upon by the regenerated sulphuric acid. The course of the reaction was explained by Williamson by the following equations

$$\text{I.}\quad C_2H_5 \cdot OH + H_2SO_4 = \underset{\text{Ethyl hydrogen sulphate}}{C_2H_5OSO_3H} + H_2O$$

$$\text{II.}\quad C_2H_5OSO_3H + HO \cdot C_2H_5 = C_2H_5 \cdot O \cdot C_2H_5 + H_2SO_4$$

Hence it would be expected that small amounts of sulphuric acid would be capable of converting unlimited quantities of alcohol into ether. In practice, however, this cannot be realised, owing to dilution of the acid by the liberated water and the incidence of by-reactions.

The crude ether thus obtained is allowed to stand for some time over quicklime to free it from water, alcohol and sulphur dioxide, after which the ether is distilled off on a water bath at 50°. In order to remove the last traces of alcohol it may be repeatedly shaken with small quantities of water, dried over calcium chloride and finally distilled over sodium.

Properties and Uses.—Ethyl ether is a colourless, extremely mobile liquid, lighter than water and of characteristic smell. It boils at 35.6° and solidifies at −113°. It is miscible in all proportions with alcohol but is only sparingly soluble in water. One volume of ether dissolves in about eleven volumes of water at 25°, and at the same time the water dissolves to some extent in the ether. A large number of carbon compounds, such as hydrocarbons and fats, are insoluble in water but dissolve readily in ether, which is therefore of great value as a solvent in organic chemistry (see p. 78). Ether burns with a luminous flame. It is highly inflammable and its vapour forms an explosive mixture with air. When inhaled for some time it brings about loss of consciousness, and like chloroform is used as an anæsthetic in surgical operations.

[1] For the catalytic preparation of ether in the dry way, see Mailhe and de Godon, *Bull. Soc.*, 1919 [iv.], **26**, 565.

Ether combines with hydro ferrocyanic, hydro ferricyanic and cobalticyanic acids According to Baeyer and Villiger,[1] this is due to the formation of a tetravalent oxygen compound

Ether unites with bromine to give an unstable crystalline compound $C_4H_{10}OBr_3$, melting at 24°

VII

Thio-alcohols and Thio-ethers

If the oxygen in an alcohol is replaced by sulphur, the resulting compound is known as a **thio alcohol, mercaptan** or **hydrosulphide** An example of this type is CH_3SH, methyl mercaptan or methyl hydrosulphide As may be seen from their properties, these compounds bear the same relation to hydrogen sulphide as the alcohols to water While strongly resembling the alcohols they also exhibit weak acidic properties, as would be expected from their derivation from hydrogen sulphide When they are treated with metallic oxides, such as mercuric oxide, the hydrogen of the —SH group is replaced by metal Hence the name mercaptan (*mercurium captans*) With mineral acids the metallic derivatives or mercaptides regenerate the free mercaptan

Mercaptans may be obtained by warming alkyl halides or salts of an alkylsulphuric acid with potassium hydrosulphide,

$$CH_3I + KSH = CH_3SH + KI$$
$$C_2H_5SO_4K + KSH = C_2H_5SH + K_2SO_4$$

by the action of phosphorus pentasulphide on alcohols,

$$5C_2H_5OH + P_2S_5 = 5C_2H_5SH + P_2O_5$$

or by the biochemical reduction of the corresponding thio-aldehydes with living yeast Thio-aldehydes are not easily prepared in the pure state, but as they are readily formed from ordinary aldehydes it is sufficient for this purpose to bring the latter under suitable conditions into an alcoholic solution of hydrogen sulphide and ammonia (ammonium sulphide), and to submit this mixture to the action of fermenting yeast[2]

Mercaptans have an extremely nauseous smell and boil at much lower temperatures than the corresponding alcohols Like hydrogen sulphide they are readily attacked by oxidising agents For example, under the influence of atmospheric oxygen they are converted into disulphides

$$2C_2H_5SH + O = C_2H_5S \cdot SC_2H_5 + H_2O$$

Nitric acid transforms them into sulphonic acids

$$C_2H_5SH + 3O = \underset{\text{Ethyl sulphonic acid}}{C_2H_5 \cdot SO_3H}$$

[1] Baeyer and Villiger, *Ber*, 1901, 34, 2688 Compare also Cohen and Gatecliff, *Proc Chem Soc*, 1904, 20, 194 McIntosh, *J Am C S*, 1908, 30, 1097 [2] C Neuberg and F Nord, *Ber*, 1914, 47, 2264 F Nord, *Ber*, 1919, 52, 1207

The presence of mercaptans may be detected by means of the intensely coloured *nitrosyl mercaptides* they form with nitrous acid[1]

Mercaptans combine with aldehydes to form mercaptals of the type of $CH_3 \cdot CH(SC_2H_5)_2$ and with ketones to form mercaptols such as $(CH_3)_2C(SC_2H_5)_2$ They also form additive compounds with unsaturated hydrocarbons[2]

Ethyl mercaptan, C_2H_5SH, commonly known as *mercaptan*, is the most important representative of this class[3] It is obtained technically from ethyl chloride and potassium hydrosulphide, and is used in the preparation of sulphonal Ethyl mercaptan is a particularly evil-smelling liquid of boiling-point 36° It dissolves sparingly in water, and in air rapidly oxidises to ethyl disulphide, $(C_2H_5)_2S_2$

Mercaptan condenses with acetone with elimination of water according to the equation,

$$\underset{\text{Acetone}}{(CH_3)_2CO} + \underset{\text{Ethyl mercaptan}}{2\,HSC_2H_5} = \underset{\text{Dimethyl diethyl-mercaptol}}{(CH_3)_2C(SC_2H_5)_2} + H_2O$$

When the product of condensation is oxidised with potassium permanganate it yields diethylsulphone-dimethylmethane (acetone-diethylsulphone), $(CH_3)_2C(SO_2C_2H_5)_2$, which is employed as a hypnotic under the name of **sulphonal** It crystallises in colourless prisms, is very sparingly soluble in water and melts at 126°

Trional, $\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>\!C(SO_2C_2H_5)_2$, of melting-point 75°, and **tetronal**, $\begin{matrix}C_2H_5\\C_2H_5\end{matrix}\!\!>\!C(SO_2C_2H_5)_2$, of melting-point 85°, are prepared in a corresponding manner to the above and possess similar properties

Thio-ethers or *alkyl sulphides*, such as methyl sulphide, $(CH_3)_2S$, are formed by heating potassium sulphide, K_2S, with methyl iodide

$$2CH_3I + K_2S = (CH_3)_2S + 2KI$$
$$2C_2H_5SO_4K + K_2S = (C_2H_5)_2S + 2K_2SO_4$$

ββ′ Dichloroethyl sulphide (*Mustard gas*), $(ClCH_2 \cdot CH_2)_2S$, has been used as a poison gas in warfare, and among other methods may be prepared by the following reaction[4]

$$2CH_2{:}CH_2 + S_2Cl_2 = (CH_2Cl \cdot CH_2)_2S + S$$

Thio ethers are neutral volatile liquids of nauseous smell With metallic salts they yield double compounds of the type $(C_2H_5)_2S,HgCl_2$

With mild oxidising agents one atom of oxygen is taken up to form *sulphoxides* Under more vigorous oxidation two atoms of oxygen enter the molecule with the formation of *sulphones*

$$(CH_3)_2S \longrightarrow (CH_3)_2SO \longrightarrow (CH_3)_2SO_2$$

[1] H Rheinboldt, *Ber*, 1927, 60, 184 [2] Posner, *Ber* 1905, 38, 646 [3] Methyl mercaptan, CH_3SH, has been isolated as a cleavage product in the fermentation of proteins [4] W J Pope, *Chem Trade Journal*, 1919, 64, 477 Smith, Clowes and Marshall, *C*, 1919, III, 622 For other poison gases see A A Fries, *C*, 1926, II, 285

Alkyl Polysulphides — If in the method given above for the preparation of thio-ethers from potassium alkyl sulphates or alkyl halides a polysulphide of potassium is exchanged for the hydrosulphide, the reaction leads to the formation of the corresponding polysulphides, such as methyl disulphide, $(CH_3)_2S_2$, and methyl trisulphide, $(CH_3)_2S_3$. These are yellow liquids of unpleasant smell, which readily undergo oxidation.

Allyl disulphide, $(C_3H_5)_2S_2$, one of the best known polysulphides, occurs together with related polysulphides in garlic.

Compounds of selenium and tellurium are also known corresponding to the foregoing sulphur derivatives. They resemble the latter in their chemical properties but are of little theoretical or practical importance.

VIII

Alkyl Nitrogen Compounds

I.—NITROSO-DERIVATIVES

Nitroso compounds are those in which the nitroso-group —N : O is united to a hydrocarbon radical, and it is only in comparatively recent times that they have been carefully investigated. They may be obtained by the following methods:—

1. By treating oximes with an oxidising agent such as bromine dissolved in pyridine, or chlorine in hydrochloric acid. The change occurs with greater ease when the carbon atom attached to the nitrogen simultaneously passes over into the tertiary condition. For instance, the reaction between acetoxime and bromine proceeds according to the equation,[1]

$$\underset{\text{Acetoxime}}{(CH_3)_2C : NOH} + Br_2 \longrightarrow \underset{\text{Bromo-nitroso-propane}}{(CH_3)_2C\begin{cases}NO\\Br\end{cases}} + HBr$$

2. By oxidising an amine containing a tertiary carbon atom with Caro's acid (monopersulphuric acid). In this manner tertiary nitrosobutane is obtained from tertiary butylamine:

$$(CH_3)_3C.NH_2 \longrightarrow (CH_3)_3C.NHOH \longrightarrow (CH_3)_3C.NO$$

3. Nitroso-compounds containing other substituents in the molecule in addition to the nitroso group are formed by the action of nitrogen peroxide, nitrogen trioxide, nitrosyl chloride or nitrosyl bromide on ethylene hydrocarbons (see p. 110).

[1] Piloty, *Ber.*, 1898, **31**, 452; 1902, **35**, 3113. On treating ketoximes with bromine in the presence of pyridine a blue coloration is produced even at high dilutions, owing to the formation of bromo-nitroso compounds. This reaction is an excellent test for the detection of aliphatic ketones, particularly acetone.

Properties.—True nitroso compounds can exist in two modifications, one of which is dimolecular, colourless and solid, and the other monomolecular, blue and often liquid. The typical nitroso-derivatives are monomolecular liquids or crystalline solids of deep blue colour. They are highly volatile and have a characteristic and usually pungent smell. The colourless crystalline dimolecular forms give blue oils on fusion, and under suitable conditions dissolve with the production of a blue solution.[1]

Nitroso-butane, $(CH_3)_3C.NO$, for example, exists as a blue compound of the formula C_4H_9NO, and as a colourless modification of the formula $C_8H_{18}N_2O_2$. In solution, the latter undergoes partial dissociation, which increases with rise of temperature.

It has also been shown that aliphatic nitroso-compounds exhibit dynamic isomerism (p. 62) as expressed in the formulæ[2]

Thus the blue monochloro nitroso-ethane readily changes into the isomeric oxime on standing at the ordinary temperature in ethereal solution

Nitroso-compounds may be oxidised to nitro-compounds and reduced to amines,

$$\underset{\text{Tertiary butylamine}}{(CH_3)_3C.NH_2} \xleftarrow{\text{Reduction}} \underset{\text{Tertiary nitroso butane}}{(CH_3)_3C.NO} \xrightarrow{\text{Oxidation}} \underset{\text{Tertiary nitro butane}}{(CH_3)_3C.NO_2}$$

The majority of them give Liebermann's nitroso reaction (see p. 162).

II.—NITRO-COMPOUNDS[3]

Nitro-derivatives of the hydrocarbons are those in which hydrogen has been replaced by the monovalent nitro group —NO_2. In all of these nitrogen is united directly to carbon, whereas in the isomeric nitrous acid esters (p. 148) it is linked indirectly through oxygen to the alkyl group.

$H_3C.NO_2$	$H_3C.O.N:O$
Nitromethane	Methyl nitrite

[1] Piloty, *Ber.*, 1902, 35, 3114; J. Schmidt, *Ber.*, 1902, 35, 2323, 3727; Bamberger and Seligmann, *Ber.*, 1903, 36, 685. [2] J. Schmidt, *Ber.*, 1902, 35, 2325; Piloty and Steinbock, *Ber.*, 1902, 35, 3104. See also Bamberger, *Ber.*, 1903, 36, 57, 317. [3] It should be noted that certain nitric acid esters prepared on a technical scale, such as nitro-glycerine and nitro-cellulose, are also frequently but incorrectly termed nitro compounds.

This difference of constitution may be deduced more particularly from the following two reactions —

1 On reduction nitro-compounds are converted into amino-compounds Under the same conditions nitrous esters yield an alcohol and ammonia

$$\underset{\text{Nitromethane}}{H_3C \cdot NO_2} + 6H = \underset{\text{Methylamine}}{H_3C \cdot NH_2} + 2H_2O$$

$$\underset{\text{Methyl nitrite}}{H_3C \cdot O \cdot NO} + 6H = \underset{\text{Methyl alcohol}}{H_3C \cdot OH} + NH_3 + H_2O$$

2 Nitro-derivatives of the hydrocarbons are not decomposed by the action of alkalis, nitrous acid esters, on the other hand, are hydrolysed to give an alkali nitrite and the corresponding alcohol

Nitro-compounds are prepared by the interaction of silver nitrite and an alkyl iodide (V Meyer),

$$C_2H_5I + AgNO_2 = C_2H_5 \cdot NO_2 + AgI$$

the corresponding alkyl nitrites being formed at the same time Since the isomers differ considerably in boiling-point they may be separated by fractional distillation Mercurous nitrite can be substituted for silver nitrite in the above reaction

Nitro-paraffins are frequently prepared from the α-halogen-substituted fatty acids On treatment with sodium nitrite these yield α-nitro-substituted fatty acids, which readily lose carbon dioxide to give nitro-paraffins In this manner nitro-methane[1] may be obtained from chloracetic acid and sodium nitrite

$$Cl \cdot CH_2COOH + NaNO_2 = NO_2 \cdot CH_2COOH + NaCl$$
$$NO_2 \cdot CH_2COOH = CH_3 \cdot NO_2 + CO_2$$

In many cases it is also possible to prepare nitro-paraffins by heating the parent hydrocarbon with dilute nitric acid[2]

In addition to those already mentioned above, the following *properties and reactions of the nitro paraffins* are of importance They are colourless, pleasant-smelling liquids, sparingly soluble in water, which distil without decomposition and boil at a much higher temperature than the corresponding isomeric esters of nitrous acid

Those nitro-compounds in which at least one hydrogen atom is attached to the carbon atom binding the nitro group, i e, *primary or secondary nitro-compounds, are acidic in character*

$$\underset{\substack{\text{Nitro ethane}\\\text{(primary)}}}{H_3C \cdot CH_2 \cdot NO_2} \qquad \underset{\substack{\text{2-Methyl-2 nitro ethane}\\\text{(secondary)}}}{(H_3C)_2 \cdot CH \cdot NO_2} \qquad \underset{\substack{\text{Tertiary nitro}\\\text{butane}}}{(H_3C)_3C \cdot NO_2}$$

In such compounds one of the hydrogen atoms in the α-position can be replaced by sodium or potassium The sodium derivatives

[1] Steinkopf and Kirchhoff, *Ber*, 1909, 42, 3438 [2] Markownikoff, *Ber*, 1900, 33, 1905 Zaloziecki and Frasch, *Ber*, 1902, 35, 386

are obtained by mixing the nitro-compound with sodium ethoxide or methoxide in alcoholic solution, salt-formation being accompanied by the simultaneous or preliminary rearrangement of the $—NO_2$ group into $=NO\cdot OH$:[1]

$$H_3C\cdot CH_2\cdot NO_2 + NaOC_2H_5 \longrightarrow H_3C\cdot CH:NO\cdot ONa + C_2H_5\cdot OH$$

The salts are therefore not derived from nitro-paraffins but from labile isomerides known as **isonitro-paraffins**. Following a suggestion of Hantzsch,[2] the latter are distinguished as the *aci*-**forms**, and the true nitro compounds as **pseudo-acids**. When the solution of an alkali salt of an *aci*-nitro-paraffin is acidified, the labile *aci*-nitro-paraffin which is first liberated changes rapidly in most cases into the nitro-paraffin.

From phenyl-nitro-methane, however, Hantzsch[3] was able to isolate both isomeric forms. The true *phenyl-nitro-methane*, $C_6H_5\cdot CH_2\cdot NO_2$, is stable in the free state, neutral and a non-conductor of electricity. It does not form salts directly, but under the influence of alkalis is converted into *aci-phenyl-nitro-methane*, $C_6H_5\cdot CH:NO\cdot OH$, which although labile in the free state yields stable metallic salts of the type of $C_6H_5\cdot CH:NO\cdot OK$. The *aci*-compound is acid, a conductor of electricity and even in the solid form changes slowly into true phenyl-nitro-methane.

The *behaviour of the nitro-paraffins towards nitrous acid* is very characteristic, and differs according as the compound is primary, secondary or tertiary. It thus serves as a means of distinguishing between these three types.

With a primary nitro compound a **nitrolic acid**[4] is obtained, which dissolves in alkalis forming a metallic derivative and giving a blood-red coloration:

$$\underset{\text{Nitro-ethane}}{H_3C\cdot C\begin{cases}H\\H\\NO_2\end{cases}} + ONOH = \underset{\substack{\text{Ethyl nitrolic acid}\\\text{(Nitro-acetaldoxime)}}}{H_3C\cdot C\begin{cases}NOH\\NO_2\end{cases}} + H_2O$$

Secondary nitro-paraffins yield **pseudo-nitrols**, which are to be regarded as nitro-nitroso compounds. They exist accordingly in two

$$\underset{\text{Nitro-propane}}{\begin{matrix}H_3C\\H_3C\end{matrix}\!\!>C<\!\!\begin{matrix}H\\NO_2\end{matrix}} + HONO = \underset{\text{Propyl-pseudo-nitrol}}{\begin{matrix}H_3C\\H_3C\end{matrix}\!\!>C<\!\!\begin{matrix}NO\\NO_2\end{matrix}} + H_2O$$

[1] This change has also been confirmed by optical measurements, *cf.* Hedley, *Ber.*, 1908, **41**, 1195. [2] *Ber.*, 1905, **38**, 1001. [3] Hantzsch and Schultze, *Ber.*, 1896, **29**, 699, 2251.

[4] The constitution of **nitrolic acids** is shown by their formation from dibromo-nitro-paraffins and hydroxylamine:

$$H_3C\cdot C\begin{cases}Br\\Br\\NO_2\end{cases} + H_2NOH = H_3C\cdot C\begin{cases}NOH\\NO_2\end{cases} + 2HBr$$

modifications (see p 154), are colourless in the solid state and on fusion or in solution develop an intense blue colour [1]

Tertiary nitro-compounds do not interact with nitrous acid at all

Since alcohols are readily converted into iodides, and these by means of silver nitrite into nitro-paraffins, it is possible by examining the behaviour of the latter towards nitrous acid to distinguish between primary, secondary and tertiary alcohols

The reaction is carried out by adding sodium nitrite followed by dilute acid to the alkaline solution of the nitro compound the solution is then made alkaline and note taken as to the development of a red coloration (nitrolic acid), a blue coloration (pseudo nitrol) or the absence of any colour change (tertiary nitro compound) The pseudo nitrol frequently separates in the solid form, in which case the blue colour is developed on bringing it into solution in chloroform or ether

On *treatment with bromine or chlorine* in the presence of alkali, primary and secondary nitro-paraffins yield halogen substitution products, in which halogen is attached to the same carbon atom as the nitro group Tertiary nitro-compounds give no chlorine or bromine derivatives under these conditions

Zinc alkyls or organo-magnesium compounds react with nitro-paraffins to form derivatives of hydroxylamine [2]

The simple **nitro-olefines** have been less investigated A typical representative of this class, *nitro-ethylene*, $CH_2 \colon CH \cdot NO_2$, may be obtained by removing the elements of water from β-nitro-ethyl alcohol, $CH_2(OH) \cdot CH_2 \cdot NO_2$, by means of P_2O_5 or sodium hydrogen sulphate [3] It is a mobile liquid, b p 98 5°, with scarcely a trace of colour Its most striking property is the powerful irritant effect it has on the mucous membrane of the eyes and respiratory organs The marked physiological and chemical similarity existing between nitro-compounds and the aldehydes and ketones led to a comparison of nitro-ethylene with acrolein, $CH_2 \colon CH \cdot CHO$, and thus to some understanding of its irritant action Nitro-ethylene also shares with acrolein a strong tendency to polymerisation, *e g*, when treated with alkali it polymerises with almost explosive violence

III —AMINES.

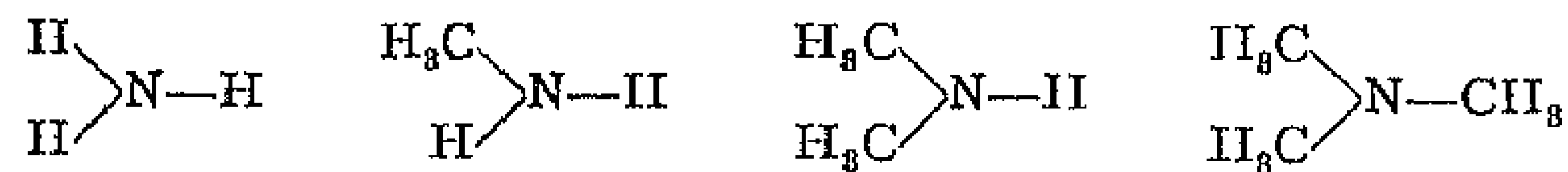
The hydrogen atoms of ammonia may be successively exchanged for alkyl groups with the formation of compounds known as amines or amine bases According as one, two or three hydrogen atoms are

[1] **Pseudo nitrols** are more conveniently prepared by the action of nitrogen peroxide on ketoximes (Scholl, *Ber*, 1888, **21**, 507 J Schmidt, *Ber*, 1900, **33**, 872) Their constitution has been proved beyond doubt by their synthesis from bromo nitroso hydrocarbons by the action of silver nitrite (Piloty and Stock, *Ber*, 1902, **35**, 3093)

$$\begin{matrix} H_3C \\ H_3C \end{matrix} \!\!> C <\!\! \begin{matrix} NO \\ Br \end{matrix} + AgNO_2 = \begin{matrix} H_3C \\ H_3C \end{matrix} \!\!> C <\!\! \begin{matrix} NO \\ NO_2 \end{matrix} + AgBr$$

[2] Moureu, *C r*, 1901, **132**, 837 Bewad, *Ber*, 1907, **40**, 3065 [3] Wieland and Sakellarios, *Ber*, 1919, **52**, 898 For phenyl nitro ethylene see Meisenheimer, *Ann*, 1907, **355**, 260.

replaced the resulting derivatives are described as *primary*, *secondary* or *tertiary amines* respectively



Ammonia	Methylamine (primary amine)	Dimethylamine (secondary amine)	Trimethylamine (tertiary amine)

All three classes of amines resemble ammonia in possessing basic properties, and like the latter combine directly with acids to form salts in which the originally trivalent nitrogen changes into the pentavalent state. Tertiary amines also combine with alkyl halides to form quaternary ammonium salts, which may be regarded as ammonium halides in which all four hydrogen atoms are displaced by alkyl groups. Corresponding to these salts are the *quaternary ammonium hydroxides* of strongly basic character, closely approximating to potassium and sodium hydroxides in their behaviour.

H_4NCl	$(H_3C)_3NHCl$	$(H_3C)_4NCl$	$(H_3C)_4NOH$
Ammonium chloride	Trimethyl ammonium chloride, or trimethyl-amine hydrochloride	Tetramethyl ammonium chloride	Tetramethyl ammonium hydroxide (a quaternary base)
		$\underbrace{\qquad\qquad\qquad\qquad\qquad\qquad}_{\text{Quaternary ammonium compounds}}$	

As will readily be understood, the amines present various possibilities of isomerism. We may meet with metamerism due to homology of the alkyl groups attached to the nitrogen atom, as in the case of trimethyl-amine, $(CH_3)_3N$, methyl-ethyl-amine, $(CH_3)(C_2H_5)NH$, and propyl-amine, $C_3H_7NH_2$, with chain isomerism, dependent on the different mode of linking of the carbon atoms in the alkyl groups, and which may therefore appear in the case of a single group of three carbon atoms, *e.g.*, propyl-amine, $CH_3 \cdot CH_2 \cdot CH_2 \cdot NH_2$, and isopropyl-amine, $(CH_3)_2CH \cdot NH_2$, and finally, if alkyl groups containing a greater number of carbon atoms are present, with position isomerism caused by the varying position of the nitrogen in one and the same carbon chain.

Formation of Amines

I. *Alkylation Methods*.—It was discovered by Hofmann that the hydrogen of ammonia is readily replaced by alkyl groups when an aqueous or alcoholic solution of ammonia is heated with alkyl halides. An atom of halogen first unites with a hydrogen atom of ammonia to form hydrogen halide, the place of the hydrogen being then taken by the alkyl residue. In this way one molecule of primary amine and one molecule of hydrogen halide are produced which combine to form the amine salt. (X stands for chlorine, bromine or iodine.)

$$1. \quad C_nH_{2n+1} \cdot X + NH_3 = C_nH_{2n+1} \cdot NH_2, HX$$

The alkyl halide next reacts with the primary amine, with the formation of a secondary amine

$$2 \quad C_nH_{2n+1}X + C_nH_{2n+1}NH_2 = (C_nH_{2n+1})_2NH, HX$$

which in a similar manner gives rise to a tertiary amine

$$3 \quad C_nH_{2n+1}X + (C_nH_{2n+1})_2NH = (C_nH_{2n+1})_3N, HX$$

Finally the latter combines with more alkyl halide to form a quaternary ammonium salt

$$4 \quad C_nH_{2n+1}X + (C_nH_{2n+1})_3N = (C_nH_{2n+1})_4NX$$

These four stages usually proceed simultaneously and lead to the formation of a mixture of all four products The ease with which the reaction occurs varies with the alkyl halide employed Owing to greater convenience of manipulation, alkyl iodides are commonly used in the laboratory, whereas on the technical scale the cheaper alkyl bromides are preferred

In most cases the separation of the mixture of amino compounds thus obtained is a difficult problem, the quaternary salt being the only product readily isolated Unlike the salts of primary, secondary and tertiary amines, the quaternary compounds are not decomposed by alkali When, therefore, a solution containing the four types of salts is treated with potassium hydroxide and distilled, the volatile amines collect in the distillate, leaving the quaternary compound behind in the distilling vessel The separation of the volatile amines may occasionally be effected by fractional distillation, but more generally one of the chemical methods described later must be employed

A convenient methylating agent, particularly for primary and secondary amines, has been found in dimethyl sulphate [1]

Another means of methylating primary and secondary amines is to treat them in acid solution with formaldehyde, at a high temperature This reaction can also be applied to ammonia and ammonium salts Under these conditions the hydrogen atoms are successively replaced by methyl groups, three molecules of formaldehyde being required for the displacement of each two atoms of hydrogen [2]

$$2NH_3 + 3H \cdot CHO = 2H_2N \cdot CH_3 + CO_2 + H_2O$$
$$2NH_3 + 6H \cdot CHO = 2HN(CH_3)_2 + 2CO_2 + 2H_2O$$
$$2NH_3 + 9H \cdot CHO = 2N(CH_3)_3 + 3CO_2 + 3H_2O$$

The formaldehyde is conveniently supplied in the form of the 40 per cent solution of commerce, and the reaction provides a simple and economical method of methylation capable of extensive application

Another method depends on the interaction between alcohols and ammonia under the catalytic influence of certain metallic oxides [3] When the vapour of ethyl alcohol mixed with ammonia is led over

[1] F Ullmann, *Ber*, 1900, **33**, 2476 *Ann*, 1903, **327**, 104 [2] Eschweiler, *Ber*, 1905, **38**, 880 [3] Sabatier and Mailhe, *C r*, 1909, **148**, 898

thoria or blue oxide of tungsten at 360°, ethylamine is obtained together with di- and tri-ethylamines

$$R \cdot CH_2OH + NH_3 = R \cdot CH_2 \cdot NH_2 + H_2O$$

II Primary amines free from admixed secondary and tertiary derivatives are formed —

(*a*) By the reduction of either nitro- or nitroso-paraffins (p 154), when alkyl-hydroxylamines are produced as intermediate products[1]

$$\underset{\text{Nitromethane}}{H_3C \cdot NO_2} \longrightarrow \underset{\beta\text{ Methyl hydroxylamine}}{H_3C \cdot NH \cdot OH} \longrightarrow \underset{\text{Methylamine}}{H_3C \cdot NH_2}$$

(*b*) By the reduction of nitriles or alkyl cyanides[2] (*Mendius reaction*)

$$\underset{\text{Acetonitrile}}{H_3C \cdot CN} + 4H = \underset{\text{Ethylamine}}{H_3C \cdot CH_2 \cdot NH_2}$$

(*c*) By boiling esters of isocyanic acid with caustic potash

$$\underset{\text{Methyl isocyanate}}{O : C : NCH_3} + 2KHO = K_2CO_3 + H_2N \cdot CH_3$$

(*d*) By the *Hofmann method*, in which bromine and potassium hydroxide are brought into reaction with acid amides The amine formed in this case contains one carbon atom less than the amide employed Acetamide, CH_3CONH_2, for example, yields methylamine, $CH_3 \cdot NH_2$

$$CH_3 \cdot CO \cdot NH_2 + Br_2 + KOH = \underset{\text{Acetbromamide}}{CH_3 \cdot CO \cdot NHBr} + KBr + H_2O$$

$$CH_3 \cdot CO \cdot NHBr + 3KOH = CH_3 \cdot NH_2 + KBr + K_2CO_3 + H_2O$$

(*e*) By *Gabriel's method*, using phthalimide (see p 445)

For the preparation of pentamethylene diamine or cadaverine from piperidine, see Braun, *Ber*, 1904, **37**, 3583, **38**, 2203

III Amines are formed in living organisms by the degradation of amino acids by elimination of CO_2, or by loss of formic acid and subsequent reduction Bacteria thus convert α-amino-isovaleric acid into isobutyl amine[3] Similarly, the important compound taurine is formed in animal organisms from cysteine (p 234)

Properties and Chemical Behaviour—As has been mentioned above, the amines strongly resemble ammonia in their power of forming salts and in many other properties The lowest members are gases, readily soluble in water and possessing an ammoniacal odour Unlike ammonia they are combustible The higher amines

[1] Primary amines are also obtained by reducing the oximes and hydrazones of aldehydes and ketones [2] It has been shown by Sabatier and Senderens (*C*, 1905, I, 860) that at 180 to 220°, in the presence of excess of hydrogen and finely divided nickel, aliphatic nitriles are generally reduced to primary amines, but these by subsequent elimination of ammonia are partially converted into secondary and tertiary amines The chief product is usually the secondary amine, the primary and tertiary derivatives being formed in approximately equal amounts. [3] C Neuberg and Karczag, *Biochem Z*, 1909, **18**, 434

are liquids which also dissolve in water, although the solubility diminishes with increase in molecular weight. Like ammonia the amines form double salts with the chlorides of certain metals, chief among which are gold and platinum (p. 11); the composition of these compounds corresponds in most cases to that of the analogous derivatives of ammonia, *e.g.*,

$$[NH_3HCl]AuCl_3 \qquad [N(CH_3)_3HCl]AuCl_3$$
$$[NH_3HCl]_2PtCl_4 \qquad [N(CH_3)_3HCl]_2PtCl_4$$

Tertiary amines also yield addition products with halogens.[1]

For the behaviour of aliphatic amines on oxidation, see p. 153, also Vorländer, *Ann.*, 1906, **345**, 241.

Amines appear to be produced in small amounts in the human body and to play an important part as "hormones" in the initiation and regulation of biological processes.

Conversion of Amines into Alcohols by Means of Yeast and Moulds.[2]—Many yeasts attack primary amines and utilise them for building up their own proteins. The assimilation proceeds in a manner similar to that of the amino acids, in that ammonia alone is split off and converted by the yeast into protein, while the hydrocarbon residue of the amine retains its identity and is found in the form of the corresponding alcohol in the fermented solution. The result of the reaction may be expressed by the equation

$$R.CH_2.NH_2 + H_2O = R.CH_2.OH + NH_3$$

Various moulds also have the power of growing in the presence of amines, and of transforming them into alcohols.

Among the many reactions by which we may distinguish between primary, secondary and tertiary amines, the following may be noted.

1. *Behaviour towards Nitrous Acid.*—Primary amines react with nitrous acid to yield the corresponding primary alcohol, with evolution of nitrogen.[3]

$$CH_3.NH_2 + ONOH = CH_3.OH + N_2 + H_2O$$

The mechanism of the process is not yet understood. Although only one molecular proportion is indicated in the equation, experiment has shown that the amine nitrite first formed only decomposes in the presence of excess of nitrous acid, the velocity varying as the product $[CH_3.NH_3^{\cdot}][NO_2'][HNO_2]$. The reaction is therefore not a simple decomposition of the amine nitrite.[4]

Secondary amines yield nitrosamines.

$$(CH_3)_2NH + HONO = (CH_3)_2N.NO + H_2O$$

This reaction is carried out by treating a concentrated aqueous solution of amine hydrochloride with a concentrated solution of potassium nitrite. The nitrosamine, which separates as an oil, may be extracted with ether and purified by distillation with steam.

[1] Hantzsch and Graf, *Ber.*, 1905, **38**, 2154. [2] Ehrlich and Pistschimuka, *Ber.*, 1912, **45**, 1006. [3] For abnormalities which may occur during this reaction, see *Ber.*, 1876, **9**, 535, and 1877, **10**, 132. [4] T. W. J. Taylor and L. Slater Price, *J.*, 1928, 1099; 1929, 2052.

Nitrosamines are yellow or yellow-red neutral oils of aromatic smell. From them the secondary bases may be regenerated by treatment with strong reducing agents or by boiling with concentrated hydrochloric acid. Nitrosamines are often of great value in the recognition and purification of secondary amines. When warmed with phenol and concentrated sulphuric acid, and then diluted with water and made alkaline with sodium hydroxide, they give an intense blue or violet coloration (*Liebermann's reaction*).[1] This colour reaction is characteristic of all nitrosamines and many other nitroso-derivatives (see p. 154).

Tertiary amines either fail to react with nitrous acid or undergo decomposition.

The above reaction may also be employed for separating secondary and tertiary amines from mixtures containing the primary compound, but in this case the latter is always destroyed.[2]

2. *Behaviour on Alkylation.*—As will be seen from the details given on p. 159, it is possible to distinguish between primary, secondary and tertiary amines by treating them with methyl iodide until the whole of the replaceable hydrogen has been displaced by methyl groups. By analysis of the base before and after treatment we may determine how many methyl groups have entered the molecule, and thus classify the original amine.

This reaction is frequently employed in investigating the constitution of alkaloids.

3. *Behaviour towards acid chlorides*, such as benzene sulphonic chloride. Primary and secondary amines interact with acid chlorides and anhydrides, an acyl group (*e.g.*, CH_3CO) being substituted for the replaceable hydrogen of the base. Tertiary amines do not react.

$$\begin{matrix} H_5C \\ H_5C \end{matrix}\!\!>\!NH \xrightarrow{CH_3 \cdot CO \cdot Cl} \begin{matrix} H_5C \\ H_5C \end{matrix}\!\!>\!N \cdot CO \cdot CH_3$$

In general it is only possible to replace one of the two typical hydrogen atoms in a primary amine by means of acetylating agents, although diacetylation may occur in certain cases.[3]

The acetyl and benzoyl derivatives are usually solid compounds of definite melting-point and are much used for the identification of amines.

On the other hand, with the aid of benzene sulphonic chloride primary, secondary and tertiary amines may be distinguished and isolated from one another. The separation depends on the fact that primary amines react with benzene sulphonic chloride to form

[1] The colour is due to the formation of an indophenol (Decker and Solonina, *Ber.*, 1902, 35, 3217), see p. 425. [2] For a method of distinguishing between primary, secondary and tertiary bases by means of 1 : 5-dibromo-pentane, see Braun, *Ber.*, 1908, 41, 2156. [3] *Ber.*, 1893, 26, 2853; 1894, 27, 93; 1901, 34, 665.

derivatives of the type $C_6H_5SO_2 \cdot NHR$, which readily dissolve in aqueous alkali, the hydrogen atom attached to nitrogen being replaceable by metals. Secondary amines on the contrary yield compounds of the type $C_6H_5SO_2 \cdot NR_2$, which are insoluble in alkali. Tertiary amines do not react at all. In some cases this method requires modification.[1]

Other reactions of primary amines are as follows: (1) With chloroform and alcoholic potash they yield isocyanides (p. 123). (2) With concentrated nitric acid they are converted into nitramines,

$$\underset{\text{Ethylamine}}{C_2H_5NH_2} + HNO_3 = \underset{\text{Ethyl nitramine}}{C_2H_5NH \cdot NO_2} + H_2O$$

The latter are solid compounds of weakly acidic nature, in which the hydrogen atom attached to nitrogen is replaceable by metals. (3) Primary amines also unite readily with aldehydes, with elimination of water:

$$CH_3 \cdot NH_2 + OCH \cdot CH_3 = CH_3 \cdot N : CH \cdot CH_3 + H_2O$$

Methylamine, $CH_3 \cdot NH_2$, is found in *mercurialis perennis* and is prepared by Hofmann's method (p. 160) from acetamide, bromine and caustic soda. It is a colourless gas with a smell resembling that of ammonia; it burns with a yellow flame and is very soluble in water.

Dimethylamine, $(CH_3)_2NH$, occurs in herring brine and is best obtained from nitroso-dimethyl-aniline by heating with caustic soda. It boils at 7°, and is a colourless liquid of ammoniacal smell.

Trimethylamine, $(CH_3)_3N$, occurs in nature in many plants, and also in herring brine. It is a liquid of boiling-point 3.5°, readily soluble in water. On the large scale it is prepared by the distillation of beet molasses or from herring brine. It is conveniently obtained in the pure state by heating ammonium chloride with formaldehyde.[2]

The salts of these amines are almost without exception readily soluble in water and alcohol.

Tetramethyl-ammonium iodide, $(CH_3)_4NI$, is a white, crystalline substance which is very sparingly soluble in alcohol. On treatment with moist silver oxide it yields tetramethyl ammonium hydroxide, $(CH_3)_4NOH$, a white, deliquescent, crystalline substance of strong basic properties:

$$(CH_3)_4NI + AgOH \rightarrow (CH_3)_4NOH + AgI$$

When heated, this decomposes into trimethylamine and methyl alcohol:

$$(CH_3)_4NOH = (CH_3)_3N + CH_3 \cdot OH$$

The more complex ammonium bases break up under the influence of heat to give water, a tertiary amine and a hydrocarbon C_nH_{2n}:

$$\underset{\substack{\text{Tetraethyl}\\\text{ammonium hydroxide}}}{(C_2H_5)_4N \cdot OH} = \underset{\text{Triethylamine}}{(C_2H_5)_3N} + \underset{\text{Ethylene}}{C_2H_4} + H_2O$$

[1] Hinsberg, *Ber.*, 1905, 38, 906; *C.*, 1906, II, 15. Vorländer and Nolte, *Ber.*, 1913, 46, 3212. [2] *Ber.*, 1905, 38, 882.

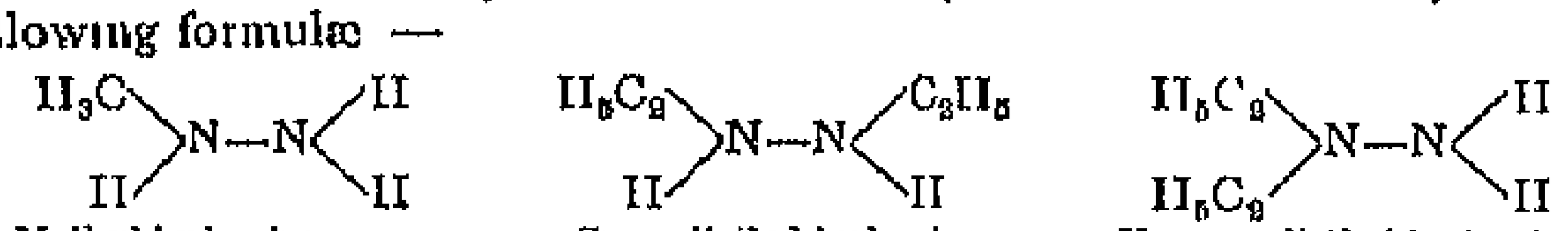
In the case of mixed amines the course of the decomposition is governed by a tendency on the one hand to split off the relatively mobile, loosely bound groups (these include the comparatively small radicals, together with allyl and benzyl), and on the other by the elimination of water to produce olefines of the highest possible degree of symmetry.[1]

By applying this reaction to cyclic amines much valuable information has been gained as to the structure of alkaloids. The study of quaternary ammonium salts has also led to considerable advances in the stereochemistry of pentavalent nitrogen.

Tetraethyl-ammonium, $N(C_2H_5)_4$, separates at the cathode as the free radical when a solution of tetraethyl ammonium chloride (or iodide) in liquid ammonia is electrolysed.[2] The blue solution first obtained gradually changes into a colourless one having the same properties. The colourless form is also produced when tetraethyl-ammonium chloride in liquid ammonia is treated with metallic potassium: $K + Cl \cdot NEt_4 = KCl + NEt_4$. The reactions of tetraethyl-ammonium are those of the alkali metals, and it may therefore be described as a *pseudo-metal*.

IV.—ALKYL HYDRAZINES AND ALKYL HYDROXYLAMINES

Alkyl-hydrazines.—As in the case of ammonia, the hydrogen atoms in hydrazine, $NH_2—NH_2$, may be substituted by alkyl groups. Alkyl hydrazines,[3] however, are of little importance and need only be described briefly. On the other hand, phenyl hydrazine (see aromatic section) is a valuable reagent. A distinction is made between primary and secondary hydrazines, the latter being again divided into those of symmetrical and unsymmetrical structure, as illustrated in the following formulæ:—



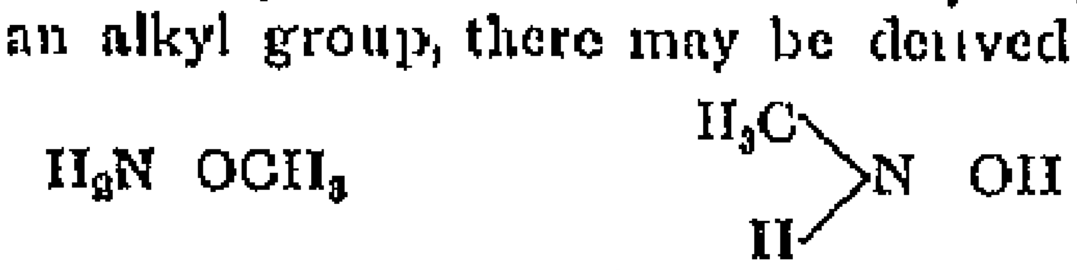
Methyl hydrazine (primary) — Sym. diethyl hydrazine — Unsym. diethyl hydrazine (secondary hydrazines)

Among other methods they are obtained by the direct alkylation of hydrazine,[4] and by the reduction of nitrosamines (p. 161):

$$(CH_3)_2N—NO \longrightarrow (CH_3)_2N—NH_2$$

For the most part they are liquid bases possessing many properties in common with the amines, but differing from them in being powerful reducing agents. With Fehling's solution, for example, they give a precipitate of cuprous oxide in the cold.

Alkyl hydroxylamines.—By the substitution of a hydrogen atom in hydroxyl amine, $NH_2 \cdot OH$, by an alkyl group, there may be derived two series of isomeric compounds, *e.g.*,



α-Methyl hydroxylamine — β-Methyl hydroxylamine

The β compounds are also formed as intermediate products during the reduction of nitro and nitroso compounds.[5]

[1] Braun, *Ann.*, 1911, 382, 1; 386, 273. [2] Schlubach, *Ber.*, 1921, 54, 2811; 1923, 56, 1889. [3] See Wieland, *Die Hydrazine* (Edited by J. Schmidt. Enke, Stuttgart 1913). [4] Harries and Haga, *Ber.*, 1898, 31, 56. [5] Bamberger, *Ber.*, 1894, 27, 1350. For further methods of preparing β compounds, see *C.*, 1899, II, 700; *Ber.*, 1901, 34, 2499; *C. r.*, 1901, 132, 837.

Aliphatic Diazo compounds

These are derived from hydrocarbons by inserting a divalent diazo group,[1] —N N—, in place of two hydrogen atoms attached to the same carbon atom. For more detailed information reference should be made to the literature.[2] The simplest representative of the series is **diazomethane**, $H_2C\left\langle{N \atop N}\right\Vert$, or $CH_2{=}N{\equiv}N$, a yellow, odourless and extremely poisonous gas. It dissolves in anhydrous ether, giving a yellow solution, and is frequently employed in this form as a methylating agent. It is prepared by warming nitroso methyl urethane with methyl alcoholic potash, the reaction taking the following course:—

$$\underset{\text{Nitroso methyl urethane}}{CH_3{\cdot}N\overset{COOC_2H_5}{\cdot}NO} \xrightarrow{KOH} \underset{\text{Potassium methyl diazotate}}{CH_3{\cdot}N{:}N{\cdot}OK} \longrightarrow \underset{\text{Diazomethane}}{CH_2\left\langle{N \atop N}\right\Vert}$$

It is also obtained by treating hydrazine with chloroform and potassium hydroxide.[3]

$$H_2N{\cdot}NH_2 + CHCl_3 + 3KOH \longrightarrow {>}C{:}N{\cdot}NH_2 + 3KCl + 3H_2O$$

$${>}C{:}N{\cdot}NH_2 \longrightarrow H_2C\left\langle{N \atop N}\right\Vert$$

Diazomethane readily decomposes with evolution of nitrogen and is a good methylating agent. For this reason it is often used to detect the presence of a labile hydroxyl group in an organic compound by converting it into the stable $\cdot OCH_3$ group. It rapidly and quantitatively converts acids into their methyl esters and phenols (p. 411) into their methyl ethers.

$$C_6H_5{\cdot}OH + CH_2N_2 = C_6H_5{\cdot}OCH_3 + N_2$$

Alcohols, under ordinary conditions, do not react with diazomethane.
Esters of aliphatic diazo acids are described later.

IX

Aldehydes, Ketones and Ketenes

General Formulae and Nomenclature.

Aldehydes and ketones are two important classes of compounds, both of which contain the carbonyl group >CO. In aldehydes the group is united on the one hand to a hydrocarbon radical and on the other to hydrogen; in ketones it is combined with two hydrocarbon radicals.

$$\underset{\text{Aldehyde}}{R{-}\overset{O}{\overset{\Vert}{C}}{-}H} \qquad \underset{\text{Simple ketone}}{R{-}\overset{O}{\overset{\Vert}{C}}{-}R} \qquad \underset{\text{Mixed ketone}}{R{-}\overset{O}{\overset{\Vert}{C}}{-}R'}$$

[1] It should be noted that diazo-compounds of the benzene series, which are treated in detail later, differ in the manner in which the diazo group is attached. [2] See Cain, *Chemistry and Technology of the Diazo Compounds* (Arnold, 1920), p. 120. Pechmann, *Ber.*, 1895, 28, 855, 1624, 2377; *Ber.*, 1898, 31, 2950; *Ber.*, 1899, 32, 2292. Hantzsch, *Ber.*, 1902, 35, 897.
[3] Staudinger and Kupfer, *Ber.*, 1912, 45, 501.

As already indicated on p 130, aldehydes are the first oxidation products of primary alcohols (hence the name aldehyde, from *alcohol dehydrogenatum*) It may be assumed that the first step in this oxidation is the formation of a compound containing two hydroxyl groups attached to a carbon atom Such derivatives, however, are unstable and generally lose water immediately to form aldehydes For example

$$\underset{\text{Ethyl alcohol}}{H_3C\ CH_2\ OH} \xrightarrow{+O} \underset{\text{Hypothetical intermediate product}}{H_3C\ CH(OH)_2} \xrightarrow{-H_2O} \underset{\text{Acetaldehyde}}{H_3C\ CH\ O}$$

The aldehydes themselves readily undergo further oxidation to yield acids containing the same number of carbon atoms

Individual aldehydes take their names from the acids produced from them on oxidation According to the Geneva nomenclature, the name of an aldehyde is obtained from that of the parent hydrocarbon by the addition of the termination *-al*

$$\underset{\text{Formaldehyde, methanal}}{H\ CHO} \qquad \underset{\text{Acetaldehyde, ethanal}}{H_3C\ CHO} \qquad \underset{\text{Isovaleraldehyde, 3 methyl-butanal}}{H_3\overset{4}{C}\ \underset{CH_3}{\overset{3}{C}H}\ \overset{2}{C}H_2\ \overset{1}{C}HO}$$

Ketones are oxidation products of secondary alcohols, and their formation may be represented in a similar manner to that of aldehydes

$$\underset{\text{Isopropyl alcohol}}{(H_3C)_2CH\ OH} \longrightarrow \underset{\text{Hypothetical intermediate product}}{(H_3C)_2C(OH)_2} \longrightarrow \underset{\text{Dimethylketone}}{(H_3C)_2CO}$$

They are far less readily oxidised than aldehydes, and as they contain no hydrogen atom attached to the carbonyl group it is not possible to obtain from them acids of the same number of carbon atoms On oxidation they generally decompose with the formation of two acids of lower carbon content

$$\underset{\text{Acetaldehyde}}{H_3C\ CHO} + O \longrightarrow \underset{\text{Acetic acid}}{H_3C\ COOH}$$

$$\underset{\text{Acetone}}{H_3C\ CO\ CH_3} + 3O \longrightarrow \underset{\text{Acetic acid}}{H_3C\ COOH} + \underset{\text{Formic acid}}{H\ COOH}$$

Ketones generally take their names from the alkyl groups present, but according to the Geneva nomenclature the names are derived from those of the parent hydrocarbons by the addition of the ending *-one* Polyketones are distinguished as *-diones*, *-triones*, and so on

$$\underset{\text{Dimethyl ketone, propanone}}{H_3C\ CO\ CH_3}, \qquad \underset{\text{Methyl-propyl ketone, pentane 2 one}}{H_3\overset{1}{C}\ \overset{2}{C}O\ \overset{3}{C}H_2\ \overset{4}{C}H_2\ \overset{5}{C}H_3}, \qquad \underset{\text{Acetyl acetone, pentane-2 4 dione}}{H_3\overset{1}{C}\ \overset{2}{C}O\ \overset{3}{C}H_2\ \overset{4}{C}O\ \overset{5}{C}H_3}$$

Formation.—In addition to the oxidation of alcohols described above, the following reactions also lead to the formation of aldehydes and ketones.

1. Dry distillation of the calcium, barium or thorium salts of carboxylic acids. In this way a ketone is produced containing two similar hydrocarbon radicals. By heating a mixture of the salts of two acids a certain proportion of the unsymmetrical ketone is obtained.

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} = CaCO_3 + \underset{\text{Dimethyl ketone}}{H_3C.CO.CH_3}$$

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} + \underset{\text{Calcium propionate}}{(H_5C_2.COO)_2Ca} = 2CaCO_3 + \underset{\text{Methyl-ethyl ketone}}{2H_3C.CO.C_2H_5}$$

If, however, the salt of a fatty acid is heated with an equivalent amount of calcium formate, the product is an aldehyde.

$$\underset{\text{Calcium acetate}}{(H_3C.COO)_2Ca} + \underset{\text{Calcium formate}}{(H.COO)_2Ca} = 2CaCO_3 + \underset{\text{Acetaldehyde}}{2H_3C.CO.H}$$

This method, involving the use of formates, is limited to the preparation of those aldehydes which distil without decomposition. Since the carboxylic acids are usually readily accessible compounds, many attempts have been made to develop general methods for their conversion into aldehydes. One such method has been found in the catalytic reduction of acid chlorides[1] (*Rosenmund*). For this purpose colloidal solutions of palladium and platinum may be employed as catalysts or, better still, the metals may be used in the finely divided state or precipitated upon some indifferent substance (*e.g.*, barium sulphate), in which form they may be separated from the reaction mixture by simple filtration (see p. 429).

Ketones may also be prepared from acids by catalytic methods, the acid or its ester being passed over thorium oxide or aluminium oxide at 300° to 380°.[2] Similarly, when a mixture of an aliphatic acid and formic acid is led in vaporous state over titanium oxide at 300° the formic acid decomposes into water and carbon monoxide, and the latter immediately reduces the aliphatic acid to the aldehyde.[3]

$$R.COOH + H.COOH = CO_2 + H_2O + R.CH:O$$

2. By the action of water on dihalogen derivatives containing the group $—CHCl_2$ or $—CHBr_2$.

$$\underset{\text{Ethylidene chloride}}{H_3C.CHCl_2} + H_2O = \underset{\text{Acetaldehyde}}{H_3C.CHO} + 2HCl$$

3. By certain reactions of the zinc alkyls and organo-magnesium compounds.

[1] Rosenmund, *Ber.*, 1918, 51, 585. [2] Senderens, *C. r.*, 1909, 148, 1211; 148, 927. [3] Sabatier and Mailhe, *C.*, 1912, I, 1290.

Zinc alkyls unite with acid chlorides to give addition products, which by treatment with water yield ketones

$$C_nH_{2n+1}\cdot C\begin{matrix}\diagup O \\ \diagdown Cl\end{matrix} + Zn\begin{matrix}\diagup CH_3 \\ \diagdown CH_3\end{matrix} = C_nH_{2n+1}\cdot C\begin{matrix}\diagup OZnCH_3 \\ -CH_3 \\ \diagdown Cl\end{matrix}$$

$$C_nH_{2n+1}\cdot C\begin{matrix}\diagup OZnCH_3 \\ -CH_3 \\ \diagdown Cl\end{matrix} + H_2O = C_nH_{2n+1}\cdot CO\cdot CH_3 + ZnO + CH_4 + HCl$$

The addition products formed from organo magnesium halides and nitriles or acid amides also react with water to give ketones

$$R\cdot CN + IMgR' = \begin{matrix}R\diagdown \\ R'\diagup\end{matrix}C\colon N\cdot MgI$$

$$2\begin{matrix}R\diagdown \\ R'\diagup\end{matrix}C\colon N\cdot MgI + 4H_2O = 2R\cdot CO\cdot R' + 2NH_3 + MgI_2 + Mg(OH)_2$$

If this reaction could be applied to the simplest nitrile, hydrogen cyanide, it could be used in the preparation of aldehydes Unfortunately this is not possible Formamide, the simplest amide, also differs in its behaviour from the higher amides and yields no aldehyde On the other hand, when formamide is replaced by disubstituted formamides the expected aldehyde is readily obtained [1]

$$H\cdot CONRR' + R''MgX = HCR''(OMgX)NRR',$$

$$HCR''(OMgX)NRR' + H_2O = R''\cdot CHO + NHRR' + Mg(OH)X$$

Aldehydes, together with secondary alcohols, may be prepared by allowing an excess of formic ester (3 mols) to interact with organo magnesium halides (1 mol) The main reaction may be expressed by the equation [2]

$$R\cdot Mg\cdot Br + H\cdot COOC_2H_5 = Br\cdot Mg\cdot OC_2H_5 + R\cdot CHO$$

4 The action of carbon monoxide on sodium alkyls yields ketones and tertiary alcohols

By treatment with diazomethane, aldehydes are in many cases converted into methyl-ketones [3]

Another useful method of preparing ketones is based on the decomposition of acetoacetic ester and its derivatives by alkalis (see acetoacetic ester)

Reactions of Aldehydes and Ketones

The behaviour of both these classes of compounds on oxidation has already been described

A number of other reactions common to aldehydes and ketones depend on their power of addition, due to the presence of the carbonyl group If the double bond in the latter is converted into a single bond, a valency is set free on carbon and oxygen, $>C=O \longrightarrow\ >\overset{|}{C}-\overset{|}{O}$ On this basis the following reactions are readily explained

[1] Bouveault, *C r*, 1903, 137, 987 [2] Gattermann and Maffezzoli, *Ber*, 1903, 36, 4152 Tschitschibabin, *Ber*, 1904, 37, 850 For additional syntheses of aldehydes by means of the Grignard reaction, see Houben, *Ch Zeit*, 1905, 667 Bouveault, *C*, 1905, I, 219 [3] F Schlotterbeck, *Ber*, 1907, 40, 479, 1909, 42, 2559 Arndt and co workers, *Ber*, 1928, 61, 1118, 1949, H Meerwein and W Burneleit, *Ber*, 1928, 61, 1840

1 On reduction with sodium amalgam, aldehydes are converted into primary alcohols and ketones into secondary alcohols

$$\underset{\text{Acetaldehyde}}{CH_3CHO} + 2H = \underset{\text{Ethyl alcohol}}{CH_3CH_2OH}, \quad \underset{\text{Acetone}}{CH_3COCH_3} + 2H = \underset{\text{Secondary propyl alcohol}}{CH_3\ CH(OH)\ CH_3}$$

Many ketones can be reduced phytochemically by fermentation with yeast, when the corresponding secondary alcohols are produced

2 Poly-halogen-substituted aldehydes and ketones unite with water to form hydrates, which are readily dehydrated again at a higher temperature

$$\underset{\text{Chloral}}{CCl_3\ CHO} + H_2O = \underset{\text{Chloral hydrate}}{CCl_3\ CH(OH)_2}$$

$$CCl_3\ CO\ CH_3 + H_2O = CCl_3\ C(OH)_2\ CH_3$$

Such aldehydes combine even more readily with alcohols to give alcoholates

$$CCl_3\ CHO + C_2H_5OH = CCl_3\ CH\begin{cases} OH \\ OC_2H_5 \end{cases}$$

When heated with excess of alcohol, particularly in the presence of dehydrating agents, aldehydes and their alcoholates yield *acetals* These may be regarded as dialkyl ethers of the (sometimes unknown) hydrate Acetals are relatively stable towards alkalis but are readily hydrolysed by hot dilute acids

$$\underset{\text{Acetaldehyde}}{CH_3\ CHO} + 2C_2H_5OH = \underset{\text{Acetal}}{CH_3\ CH(OC_2H_5)_2} + H_2O$$

Ketones form no alcoholates and only under special conditions acetals

3 Aldehydes and ketones unite with sodium bisulphite to give crystalline addition compounds, by means of which they may be purified On warming these with dilute acids or alkalis the aldehyde or ketone is again set free

$$CH_3\ CHO + NaHSO_3 = CH_3\ CH\begin{cases} OH \\ O\ SO_2Na \end{cases}$$

4 Ammonia combines with acetaldehyde according to the equation [1]

$$CH_3\ CHO + NH_3 = \underset{\text{Aldehyde-ammonia}}{C_2H_4ONH_3}$$

but this reaction is not so general as those mentioned above Formaldehyde, for example, behaves in a different manner Where simple addition occurs, the reaction is sometimes used with advantage in the purification of the aldehyde By filtering off the crystalline double compound and warming it with dilute sulphuric acid, the aldehyde is once again set free

[1] The molecular formula of aldehyde ammonia at the ordinary temperature is three times the empirical formula

Instead of forming addition compounds with ammonia the ketones yield peculiar condensation products [1]

5 Both aldehydes and ketones combine with hydrogen cyanide to form cyanhydrins

$$CH_3\ CHO + HCN = CH_3\ CH\begin{matrix} \diagup OH \\ \diagdown CN \end{matrix}$$

Aldehyde cyanhydrin or nitrile of α-hydroxy propionic acid

$$(CH_3)_2CO + HCN = (CH_3)_2C\begin{matrix} \diagup OH \\ \diagdown CN \end{matrix}$$

Acetone cyanhydrin

This reaction, in which a new carbon atom is added to the molecule, is of value in the synthesis of α-hydroxy-acids and α-amino-acids, as will be illustrated later

Acetone cyanhydrin [2] may be obtained in good yield by adding acetone to a solution of potassium cyanide and allowing sulphuric acid (30 per cent) to run in slowly with stirring, ice being added to keep the temperature below 20° The cyanhydrin is then extracted with ether, dried and distilled rapidly B p , 81°/15 mm

Recently cyanhydrins have been used extensively as the starting-point in the preparation of other substances They may also be prepared by the following reaction [3] The aldehyde or ketone, or a mixture containing one of these substances, is treated with concentrated sodium bisulphite solution, and the addition product, after separation from impurities, is allowed to interact with potassium cyanide

$$\begin{matrix} R \diagdown \\ R' \diagup \end{matrix} C \begin{matrix} \diagup OH \\ \diagdown SO_3Na \end{matrix} + KCN = \begin{matrix} R \diagdown \\ R' \diagup \end{matrix} C \begin{matrix} \diagup OH \\ \diagdown CN \end{matrix} + KNaSO_3$$

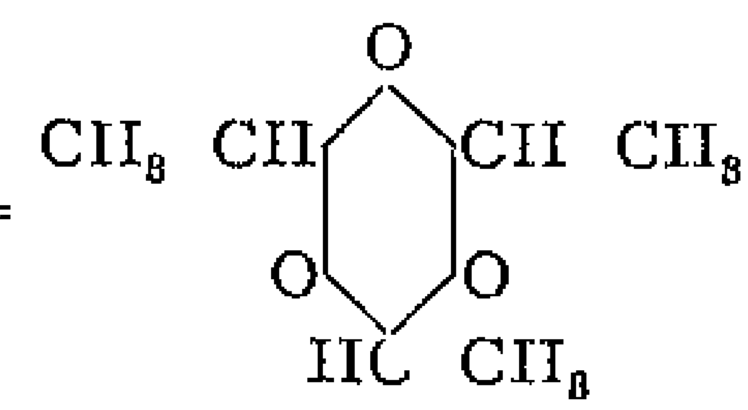
6 Aldehydes and ketones also combine with alkyl magnesium halides, as described on p 134

7 Aldehydes have a strong tendency to undergo *polymerisation* This may take place in two ways, as illustrated in the case of acetaldehyde

(*a*) When acetaldehyde, a liquid which boils at 22°, is mixed with concentrated sulphuric acid, polymerisation occurs with the evolution of much heat and the formation of a compound called paraldehyde, of boiling-point 124° From vapour density determinations the molecular weight of paraldehyde is found to be three times that of aldehyde Paraldehyde no longer shows the typical aldehyde reactions but is readily transformed into acetaldehyde by distillation with dilute sulphuric acid From these properties it may be concluded that, in the formation of paraldehyde, three molecules of aldehyde combine

[1] See Thomae, *C*, 1905, II, 115, 540, 555 [2] K W Welch and G R Clemo, *J*, 1928, 2629 [3] Bucherer and Grolée, *Ber* , 1906, 39, 1224

together in such a manner that the carbon of one molecule always unites with the oxygen of a second

$3CH_3 \cdot CH : O =$ 

Acetaldehyde Paraldehyde[1]

(*b*) Polymerisation of a quite different kind is undergone by aldehydes under the influence of small amounts of dilute alkali. Under these conditions acetaldehyde yields a compound of the same empirical composition but of twice the molecular weight. The new compound contains an open chain of four carbon atoms, as is shown by its behaviour on oxidation, and it cannot be changed back into the original aldehyde by any simple method. In this case two molecules of aldehyde have combined with the simultaneous formation of a new carbon to carbon linking

$$H_3C \cdot CHO + HCH_2 \cdot CHO = H_3C \cdot CH(OH) \cdot CH_2 \cdot CHO$$

Aldol.

Such a union is much more stable than the carbon to oxygen bond in paraldehyde, and polymerisation of this type is often termed *condensation*. The distinction between polymerisation and condensation is, however, somewhat vague, although in general the latter implies the formation of a comparatively stable product. A condensation may occur, not only as in these examples, by direct combination to yield a polymer of the original compound, but the reaction may proceed in other cases with elimination of water, alcohol, ammonia, etc., to form a condensation product which is no longer a polymer of the starting material (see Claisen condensation, p. 257 *et seq.*, and mesitylene from acetone, p. 372). The combination of two or more *different substances* to give a stable product, with or without loss of water, etc., is also frequently described as a condensation.

Combination of this type between two aldehyde molecules is known as the *aldol condensation*[2]. The same reaction may also take place between two different aldehydes, two ketones, or between an aldehyde and a ketone. The resulting aldehyde alcohols or ketonic alcohols readily split off water and pass into unsaturated aldehydes or ketones, *e.g.*

$$\underset{\text{Aldol}}{CH_3 \cdot CH(OH) \cdot CH_2 \cdot CHO} = \underset{\text{Crotonaldehyde}}{CH_3 \cdot CH : CH \cdot CHO} + H_2O$$

Many aldehydes on warming with alkalis are transformed into brown complex resinous products (*aldehyde resins*).

The great reactivity of aldehydes and ketones is by no means limited to the additive reactions illustrated. A large number of other

[1] For metaldehyde see p. 176. With regard to the polymerisation of other aldehydes, compare Franke and Wozelka, *Monats.*, 1912, 33, 349. [2] The term aldol is derived from aldehyde alcohol, the resulting compounds being both aldehydes and alcohols.

reactions common to both classes depend on their power of exchanging the oxygen of the carbonyl group for other atoms or groups

Thus, by the action of phosphorus pentachloride, oxygen may be substituted by two atoms of chlorine

$$CH_3\cdot CHO + PCl_5 = \underset{\text{Ethylidene chloride}}{CH_3\cdot CHCl_2} + POCl_3$$

Aldehydes and ketones unite with hydrazines to form *hydrazones*, water being eliminated *Phenyl-hydrazine* is usually employed for this purpose

$$H_3C\cdot CHO + \underset{\text{Phenyl hydrazine}}{H_2N\cdot NH\cdot C_6H_5} = \underset{\text{Acetaldehyde phenyl hydrazone}}{H_3C\cdot CH:N\cdot NH\cdot C_6H_5} + H_2O$$

$$(H_3C)_2CO + H_2N\cdot NH\cdot C_6H_5 = \underset{\text{Acetone phenyl hydrazone}}{(H_3C)_2C:N\cdot NH\cdot C_6H_5} + H_2O$$

This reaction, which was first applied to acetaldehyde and benzaldehyde by E Fischer, is frequently of great service in the isolation and purification of aldehydes and ketones, since the phenyl-hydrazones usually crystallise well, and on heating with hydrochloric acid take up the elements of water to regenerate the original aldehyde or ketone The phenyl hydrazone is most readily formed in weak acetic acid solution, and is commonly prepared by use of a mixture of equal volumes of phenyl-hydrazine and 50 per cent acetic acid, diluted with six volumes of water *Semicarbazide*, $NH_2\cdot CO\cdot NH\cdot NH_2$, has also proved of great value for the isolation and identification of aldehydes and ketones, the *semicarbazones* obtained being in most cases even more readily crystallisable than the corresponding phenyl-hydrazones [1]

Hydrazones and semicarbazones are converted into hydrocarbons on heating with sodium ethoxide, the reaction taking the following course —

$$>C:N\cdot NH\cdot CONH_2 + H_2O = >C:N\cdot NH_2 + CO_2 + NH_3$$

$$>C:N\cdot NH_2 = >CH_2 + N_2$$

We have here a general method of replacing the oxygen atom of a ketone or aldehyde with hydrogen [2]

Hydroxylamine, NH_2OH, combines with aldehydes and ketones in the same manner as phenyl-hydrazine, water being split off and the residue :N·OH taking the place of the oxygen The resulting compounds are termed *oximes* and are distinguished as aldoximes or ketoximes, according as they are derived from aldehydes or ketones

$$CH_3CH:O + NH_2OH = \underset{\text{Acetaldoxime}}{CH_3CH:N\cdot OH} + H_2O$$

$$(CH_3)_2C:O + NH_2OH = \underset{\text{Acetoxime}}{(CH_3)_2C:N\cdot OH} + H_2O$$

[1] See Baeyer, *Ber*, 1894, **27**, 1918, 1898, **31**, 2199

[2] J Wolff, *Ann*, 1912, **394**, 86

As in the case of the hydrazones, the oximes regenerate the original aldehyde or ketone on being heated with hydrochloric acid. The oximes possess basic as well as acidic properties, forming compounds of the type $CH_3 \cdot CH : NOH, HCl$ and $CH_3 \cdot CH : NOK$. They usually crystallise well and are also used for the isolation and identification of aldehydes and ketones.

An interesting decomposition of aldoximes, to which reference is made later, is their tendency to break up under certain conditions to form water and a nitrile.

Aldoximes are prepared by treating the aldehyde (1 mol.) with an aqueous solution of hydroxylamine hydrochloride (1 mol.) and sodium carbonate ($\frac{1}{2}$ mol.) in the cold. In the case of aldehydes insoluble in water, an aqueous alcoholic solution is employed.

The formation of a ketoxime generally occurs less readily. An aqueous or alcoholic solution of the ketone may be treated with the calculated amounts of sodium acetate and hydroxylamine hydrochloride, and heated one to two hours on the water bath; or an alcoholic solution of the compound may conveniently be sealed up in a tube with hydroxylamine hydrochloride, and heated for eight to ten hours at 160° to 180°. In the latter case, however, intramolecular rearrangement sometimes takes place and the expected oxime is not obtained.

Under the influence of phosphorus pentachloride (and of other reagents such as acetyl chloride, benzene-sulphonic chloride, and solutions of hydrochloric or sulphuric acid in glacial acetic acid),[1] the ketoximes undergo molecular rearrangement and are converted into acid amides (*Beckmann rearrangement*). For example,

$$\underset{\text{Methyl-propyl-ketoxime}}{\begin{matrix} CH_3 \\ CH_3 \cdot CH_2 \cdot CH_2 \end{matrix}\!\!>C : NOH} \longrightarrow \underset{\text{Acetpropylamide}}{\begin{matrix} CH_3 \cdot CO \\ CH_3 \cdot CH_2 \cdot CH_2 \end{matrix}\!\!>NH}$$

Under this treatment stereoisomeric ketoximes yield different products and the Beckmann reaction has therefore been employed by Hantzsch as a general means of determining the structure of these compounds. (For further details see p. 58.)

It has already been mentioned (p. 57) that the oximes were one of the first groups of stereoisomeric nitrogen derivatives to be discovered.

On reduction both aldoximes and ketoximes are converted into primary amines:

$$CH_3 \cdot CH : NOH + 4H = CH_3 \cdot CH_2 \cdot NH_2 + H_2O$$
$$(CH_3)_2C : NOH + 4H = (CH_3)_2CH \cdot NH_2 + H_2O$$

Aldehydes and ketones also give condensation products with compounds of the general formula $X \cdot CH_2 \cdot X'$ (such as aceto-acetic ester), in which X and X′ represent "reactive" groups. Compare Knoevenagel, *Ber.*, 1904, 37, 4462.

For amino aldehydes see Wohl, *Ber.*, 1905, 38, 4154, and for amino ketones see Gabriel, *Ber.*, 1911, 44, 57.

[1] Werner and Piguet, *Ber.*, 1904, 37, 4295; *Ber.*, 1905, 38, 69. For a theoretical discussion of the Beckmann change, see Schroeter, *Ber.*, 1909, 42, 3356; Stoermer, *Ber.*, 42, 3133; Montagne, *Ber.*, 1910, 43, 2014.

Detection of Aldehydes

(*a*) As already stated, aldehydes are very easily oxidised, and therefore possess reducing properties by means of which they may be detected. Thus, on treating a moderately dilute solution of an aldehyde with an ammoniacal solution of silver nitrate a more or less brilliant silver mirror is obtained, the formation of which may be hastened by gentle warming. Aliphatic aldehydes differ from those of the aromatic series in rapidly reducing Fehling's solution, with precipitation of red cuprous oxide.

(*b*) A solution of rosaniline hydrochloride which has been decolorised by sulphur dioxide (Schiff's reagent) gives an intense reddish-violet colour[1] with aldehydes.

(*c*) An aqueous solution of the sodium salt of nitro-hydroxylaminic acid reacts with a large number of aldehydes to give hydroxamic acids. On subsequent addition of ferric chloride a red coloration is produced. This permits of the detection of very small quantities of an aldehyde.[2]

For the *detection of ketones* by the conversion of ketoximes into bromo nitroso compounds, see p. 153 and footnote.

SATURATED ALDEHYDES

Formaldehyde, *methanal*, H.CH:O, is formed by the oxidation of methyl alcohol, *e.g.* when the vapour of methyl alcohol mixed with air is led over heated catalysts such as silver, copper or platinum black. It can also be prepared by oxidising ethylene (preferably diluted with nitrogen or methane) with gaseous oxygen in the presence of catalysts.[3]

Following on the discovery of Butlerow that formaldehyde could be condensed to a sugar, Baeyer suggested that in plants containing chlorophyll the conversion of carbon dioxide into carbohydrate takes place by way of formaldehyde as an intermediate. An important advance was made when Baly, Heilbron and Barker[4] showed that carbon dioxide in aqueous solution containing suspended coloured catalysts (*e.g.* colloidal uranium hydroxide) is converted by ordinary visible light into formaldehyde, and the latter into reducing sugars. Formaldehyde has since been isolated from various plants, but only from tissue containing chlorophyll which had been exposed to light.[5] Hence it appears very probable that formaldehyde is actually an intermediate product in the conversion of carbon dioxide into carbohydrates and other plant products. By means of the aldol condensation (see p. 171) the formaldehyde may then be converted into sugar, starch, cellulose

[1] For the nature of these coloured compounds, see Wieland and Scheuing, *Ber.*, 1921, 54, 2527. [2] Baudisch and Coert, *Ber.*, 1912, 45, 1775; Steinkopf and Jürgens, *J. pr. Ch.* (2), 1911, 84, 686. [3] Willstätter and Bommer, *Ann.*, 1921, 422, 36. [4] *J. C. S.*, 1921, 119, 1025. [5] G. Klein and O. Werner, *Biochem. Zeit.*, 1926, 168, 361.

or resinous products.[1] Generally speaking, all life depends on this reduction of carbon dioxide in the chloroplast under the influence of sunlight.

Pure formaldehyde is a gas at ordinary temperatures, and condenses under strong cooling to a colourless liquid of b.p. −21°. It possesses a pungent, penetrating smell, and is a powerful disinfectant. It is readily soluble in water and comes on to the market as a 40 per cent. solution, under the name of *formalin*. The latter usually contains from 12 to 18 per cent. of methyl alcohol, which is introduced during the process of manufacture and serves to prevent the formation of a sediment. Formaldehyde is a weakly acidic compound and yields salts with strong bases.

It very readily undergoes polymerisation, and several *polymeric modifications* are known. On evaporating an aqueous solution of formaldehyde a white crystalline mass of *paraformaldehyde* or *oxymethylene*, possibly of the formula $(CH_2O)_2$, is left behind. When this is heated formaldehyde is regenerated, showing that we are dealing with a case of polymerisation. Under different conditions a second polymer, *metaformaldehyde* or *trioxymethylene*,[2] $(CH_2O)_3$, may be formed. Trioxymethylene is an indefinite crystalline mass, m.p. 171° to 172°, which is insoluble in water.

Under the influence of alkalis, formaldehyde may either undergo the Cannizzaro reaction (p. 430) to give a mixture of formic acid and methyl alcohol, or a polymeride may be produced.[3]

Finally, the formaldehyde molecules may react together in a third manner. When an aqueous solution of formaldehyde is treated with lime water or magnesium hydroxide, six molecules of the aldehyde condense with the production of "formose," a mixture of sugars of the formula $C_6H_{12}O_6$ (see Sugars). It is this case of polymerisation or condensation which enables formaldehyde to play such an important part in the assimilation of plants.

In addition to its use as a disinfectant, formaldehyde is also employed for the preservation of anatomical preparations, since it possesses the property of transforming proteins into a hard elastic mass, insoluble in water. Further, it is extensively utilised in the preparation of diphenyl-methane derivatives for the manufacture of dye-stuffs, as will be described later.

When treated with ammonia, formaldehyde does not yield an aldehyde ammonia, but gives a complex substance, hexamethylene tetramine or *urotropine* $(CH_2)_6N_4$,[1] which is employed medicinally as an internal disinfectant, especially for the urinary canal. The disinfectant properties possibly depend on the liberation of formaldehyde.

[1] Willstätter, *Ber.*, 1917, 50, 1777; *Untersuchungen über die Assimilation der Kohlensäure* (Springer, Berlin, 1918). Willstätter, *Z. ang. Ch.*, 1919, 32, 329. [2] On treatment with concentrated sulphuric acid this is converted into an isomeric α-trioxymethylene, m.p. 60° to 61°. [3] Mannich, *Ber.*, 1919, 52, 160. [1] For the constitution of hexamethylene tetramine, see Duden and Scharff, *Ann.*, 288, 218.

Osmium brings about a decomposition of formaldehyde into methyl alcohol and carbon dioxide, $3H \cdot CHO + H_2O = CO_2 + 2CH_3OH$ [1]

Methylal, methylene dimethyl ether, $CH_2(OCH_3)_2$, is frequently used in place of formaldehyde for condensations and is a very good solvent for many organic compounds It may be prepared by cautious oxidation of methyl alcohol with manganese dioxide and sulphuric acid, or by the action of sodium methoxide on methylene iodide It is a pleasant smelling liquid of b p 42°

Formaldehyde condenses with phenols (p 411) to form a hard resinous product (*bakelite*) which is utilised as an insulating material, the products obtained by reaction with phenol and naphthalene sulphonic acids are employed as artificial tannins (*neradol*) With casein, formaldehyde yields a tough horny mass used as artificial horn or ivory (*galalith, etc*)

Formaldehyde sodium sulphoxylate (*rongalite C, hydraldite*) is a reducing agent employed in vat dyeing It may be prepared from formaldehyde and sodium hydrosulphite in alkaline solution

$$H \cdot CHO + NaHSO_3 + 2H_2O = HC\begin{cases}H \\ OH \\ OSONa\end{cases} + 2H_2O$$

Acetaldehyde, *ethanal*, $CH_3 \cdot C\begin{cases}O \\ H\end{cases}$ generally known as aldehyde, is formed by the methods indicated above, and is prepared by the oxidation of ethyl alcohol with sodium bichromate and sulphuric acid It is also obtained as a by-product in the manufacture of alcohol (see p 139) The conversion of acetylene into acetaldehyde under the catalytic influence of mercury salts has been known for many years and has recently been successfully employed in the manufacture of acetic acid (p 118) Acetaldehyde is a colourless, mobile liquid of peculiarly suffocating smell It boils at +21°, melts at −121°, and is readily soluble in water, alcohol and ether The presence of small amounts of acetaldehyde is best confirmed by condensation with dimethyl cyclohexanedione [2]

The most important polymerisations of acetaldehyde have already been described on pp 170, 171, but it may be added that it also polymerises under the influence of acids at temperatures below 0° to give *metaldehyde* The latter forms long, glistening crystals which sublime without melting at 115°, being partially converted into ordinary aldehyde For a long time metaldehyde was believed to be stereoisomeric with paraldehyde, but later investigation has shown it to be a polymeride [3] and not a stereoisomeride of this compound

The following derivatives of acetaldehyde are of importance —

Acetal, $CH_3 \cdot CH(OC_2H_5)_2$, b p 104°, is formed together with aldehyde by the oxidation of alcohol It is frequently used in place of aldehyde for condensation reactions

Trichloro acetaldehyde, chloral, $CCl_3 \cdot CHO$, is obtained when chlorine is led into alcohol, first with cooling and finally at a higher

[1] E Müller, *Ber*, 1921, **54**, 3214 *Zeit physik Chem*, 1923, **107**, 347 [2] D Vorländer, *Zeit für ang. Chem*, 1929, **42**, 46 [3] Hantzsch and Oechslin, *Ber*, 1907, **40**, 4341

temperature, and the crystalline product of reaction distilled with sulphuric acid. It may be assumed that the first step is the conversion of alcohol into aldehyde, chlorine acting here as an oxidising agent, followed by substitution and the formation of chloral. Chloral is an oily liquid, b.p. 97°, possessing a characteristic odour. On treatment with alkali at the ordinary temperature it decomposes into chloroform and formic acid

$$\begin{matrix} CCl_3.CHO \\ H.OK \end{matrix} = CHCl_3 + HCOOK$$

Chloral hydrate, $CCl_3.CH(OH)_2$, is produced by the action of water on chloral; it forms readily soluble crystals, m.p. 57°, and is used as a soporific. From the theoretical standpoint it is of interest as being one of the few compounds containing two OH groups bound to the same carbon atom.

Lactaldehyde, $CH_3.CHOH.CHO$, crystallises in needles, m.p. 105°.

UNSATURATED ALDEHYDES

Unsaturated aldehydes show on the whole the same chemical reactivity as the saturated compounds, but owing to the presence of multiple bonds they also undergo those additive reactions characteristic of the unsaturated hydrocarbons. They are formed, among other reactions, by molecular rearrangement from tertiary acetylenic alcohols.[1]

Acrolein, *propenal*, acrylic aldehyde, $CH_2:CH.CHO$, is prepared by removing the elements of water from glycerol by means of potassium bisulphate or boric acid.[2] In place of the potassium bisulphate commonly employed as catalyst, any sulphate may be used which yields free sulphuric acid at a comparatively low temperature. The highest and purest yields of acrolein are given by passing the vapour of glycerol over heated magnesium sulphate.[3]

$$CH_2(OH).CH(OH).CH_2(OH) = CH_2:CH.CHO + 2H_2O$$

It is a colourless liquid, b.p. 52°, which is difficultly soluble in water and has an extremely unpleasant pungent smell. The tendency of acrolein to polymerise is so great that it usually changes in a short time into a white, flocculent compound called *disacryl*. Acrolein is readily oxidised, even in the air, to form acrylic acid. Catalytic hydrogenation in the presence of nickel at 50° to 60° converts it into *propionaldehyde*.

Crotonaldehyde, $CH_3.CH:CH.CHO$, is produced by heating aldehyde with dil. hydrochloric acid, or with a solution of sodium acetate, aldol being formed

$$2CH_3.CHO \longrightarrow CH_3.CH(OH).CH_2.CHO \longrightarrow CH_3.CH:CH.CHO$$

as an intermediate product. It is a pungent smelling liquid, b.p. 105°, which on oxidation is transformed into solid crotonic acid.

[1] H. Rupe and co-workers, *Helv. chim. Acta*, 1928, **11**, 49. [2] *Ber.*, 1899, **32**, 1352; *Ber.*, 1902, **35**, 1136; *J. pr. Ch.* (2), 1905, **71**, 174; Bergh, *J. pr. Ch.* (2), 1909, **79**, 351. [3] Wohl and Mylo, *Ber.*, 1912, **45**, 2046.

$\alpha\beta$-Hexenic aldehyde, $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH : CH \cdot CHO$, is a constituent of green plants and has been isolated from beech leaves[1] as a colourless oil of peculiar smell, b p 47° to 48° under 17 mm pressure

Citral, geranial, $(CH_3)_2C : CH \cdot CH_2 \cdot CH_2 \cdot C(CH_3) : CH \cdot CHO$, b p 226°, is an important unsaturated aldehyde characterised by a pleasant smell It is closely related to geraniol and occurs in various essential oils The most convenient source of preparation is lemon-grass oil On being heated with aqueous potassium carbonate, citral takes up a molecule of water and decomposes into *methyl-heptenone* and acetaldehyde

$$\underset{\text{Methyl heptenone}}{(CH_3)_2C : CH \cdot CH_2 \cdot CH_2 \cdot CO \cdot CH_3} + \underset{\text{Acetaldehyde}}{CH_3 \cdot CHO}$$

Citral occurs in α and β isomerides (*cis* and *trans* forms) When reduced it yields geraniol together with some nerol (p 145), and both of these alcohols on oxidation are converted into citral It is used in the manufacture of the perfumes, α- and β-*ionones* (see next page)

KETONES

Acetone, *dimethyl-ketone, propanone,* $CH_3 \cdot CO \cdot CH_3$, is prepared industrially from raw wood spirit (see p 135), and by the dry distillation of calcium acetate In recent years a fermentation process involving the use of *Bacillus macerans* has been developed for the technical preparation of acetone from starch Acetone occurs in small quantities in blood and normal urine, and in larger quantities in the urine of diabetic patients (*cf* p 183). It is a liquid of pleasant smell which boils at 56° and solidifies at −94° With water, alcohol and ether it is miscible in all proportions The most important reactions of acetone have already been described on p 168 *et seq* Acetoxime forms white prisms, m p 69° By the action of nitrous acid, acetone is converted into *iso nitroso acetone*, $CH_3 \cdot CO \cdot CH : N \cdot OH$

Acetone is an excellent solvent for a variety of organic compounds, it enters into the manufacture of smokeless powder and cordite, and forms the starting material in the production of chloroform, bromoform, iodoform, sulphonal and synthetic rubber

The condensation of acetone leads to the formation of *unsaturated ketones*[2] These compounds, which have not yet been fully investigated, combine the properties of the ketones with those of the ethylene series Thus they unite with ozone to form unstable ozonides

Mesityl oxide, $(CH_3)_2C{=}CH \cdot CO \cdot CH_3$, a colourless liquid, b p 122°, with a smell resembling that of peppermint, and **phorone,** $(CH_3)_2C{=}CH \cdot CO \cdot CH{=}C(CH_3)_2$, m p 28° and b p 196°, are produced together by treating acetone with dehydrating agents such as hydrochloric acid, concentrated sulphuric acid or zinc chloride More vigorous treatment with concentrated sulphuric acid carries the process further, yielding the aromatic hydrocarbon **mesitylene** (p 372)

[1] Curtius and Franzen, *Ann*, 1912, 390, 89

[2] Knoevenagel and co workers, *Ber*, 1906, 39, 3462

Pseudo-ionone, $C_{13}H_{20}O$, is formed by the condensation of citral with acetone under the influence of baryta water,

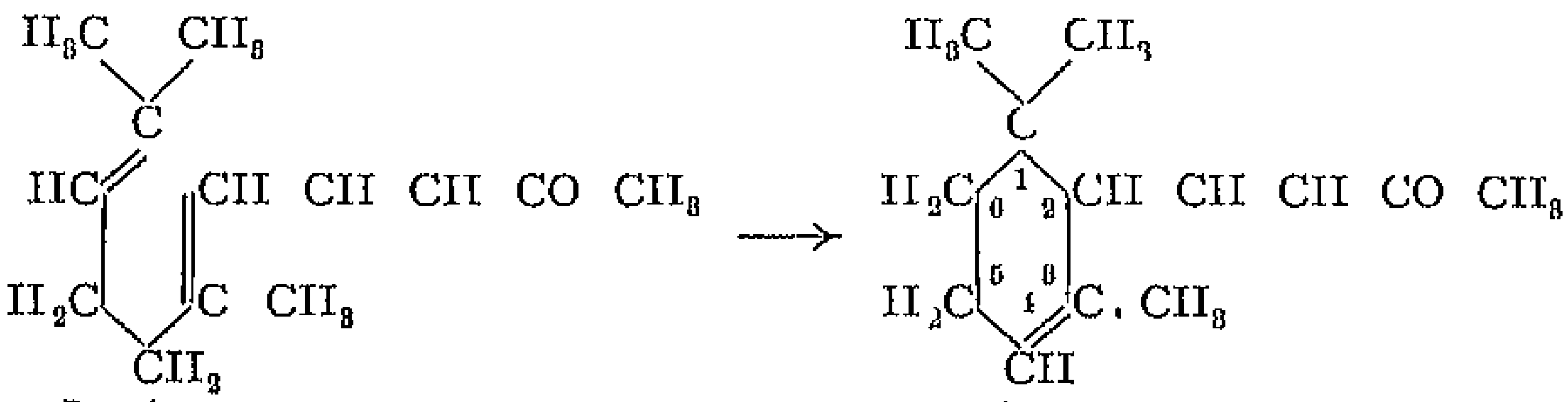
$$(CH_3)_2C\ CH\ CH_2\ CH_2\ C(CH_3)\ CH\ CHO + H_3C\ CO\ CH_3 \longrightarrow$$

Citral Acetone

$$(CH_3)_2C\ CH\ CH_2\ CH_2\ C(CH_3)\ CH\ CH\ CH\ CO\ CH_3 + H_2O$$

Pseudo ionone

When boiled with dilute sulphuric acid it is readily transformed into the isomeric ionones The latter are reduced benzene derivatives which occur in two modifications as α- and β-**ionones**, having the double bonds in the ring in the Δ^3 and Δ^2 positions respectively



Pseudo ionone   α Ionone

Isomeric with the ionones is **irone** (double bond in Δ^5-position?) which occurs in orris root and gives rise to the pleasant perfume of the violet As ionone strongly resembles irone in smell, it is prepared on a technical scale by the above method, citral or preferably lemon-grass oil being treated with acetone in the presence of an alkali (*e g*, sodium ethoxide) and the pseudo-ionone so formed converted into ionone by means of sulphuric acid or sodium bisulphate

KETENES[1]

The aliphatic series has recently been extended by the addition of a new class of compounds termed ketenes These include the simple ketene CH_2 CO discovered by Wilsmore, substituted ketenes discovered by Staudinger, who also noted their extraordinary reactivity, and the double ketene of Diels, O C C C O, somewhat inaccurately called carbon suboxide All these compounds contain tetravalent carbon The characteristic group of the ketenes is $>$C C O, and although they show none of the typical carbonyl reactions, they are here on formal grounds classed with the ketones

Preparation—The majority of ketenes of the general formula R_2C C O have been prepared according to the method of Staudinger by acting on α-halogen-substituted acid chlorides with metals, preferably zinc, in hydroxyl-free solvents In this manner dimethyl-ketene is obtained from dimethyl-bromacetyl bromide

$$(CH_3)_2CBr\ COBr + Zn = (CH_3)_2C\ CO + ZnBr_2$$

[1] See *Die Ketene* by H Staudinger, edited by J Schmidt (Enke, Stuttgart, 1912) Also Staudinger and co workers, *Helv Chim Acta*, 1918 1924

In addition, ketenes are also obtained by the disruption of ring compounds and of diazomethane derivatives. The fission of diketo-cyclobutane derivatives, which are themselves dimolecular polymerisation products of the ketenes, is an example of the former type:

$$\begin{array}{c} R_2C\text{—}CO \\ \vert \quad\;\; \vert \\ OC\text{—}CR_2 \end{array} \longrightarrow \begin{array}{c} R_2C{:}CO \\ + \\ OC{:}CR_2 \end{array}$$

The simplest ketene, $CH_2{:}CO$, is readily prepared[1] by passing the vapour of acetone at dull red heat through a glass tube filled with broken tile, when ketene and methane are formed:

$$CH_3COCH_3 = H_2C{:}CO + CH_4$$

Properties and Reactions.—The ketenes, $R_2C{:}C{:}O$, belong to the large class of compounds containing two adjacent double bonds in the molecule, and are thus to be grouped with carbon dioxide, $O{:}C{:}O$, isocyanates, $RN{:}C{:}O$, and mustard oils, $RN{:}C{:}S$. With these they possess a number of reactions in common, although differing in their yellow colour. Thus ketenes react with water, alcohols, ammonia, amines and phenyl-hydrazine, when addition occurs at one of the double bonds, leaving the other unattacked, with the formation of acids or their derivatives:

$$R_2C{:}C{:}O + HOH = R_2CH{\cdot}C\begin{array}{l} \diagup\!\!\!\!O \\ \diagdown OH \end{array}$$

$$R_2C{:}C{:}O + HNH_2 = R_2CH{\cdot}C\begin{array}{l} \diagup\!\!\!\!O \\ \diagdown NH_2 \end{array}$$

In some respects, however, the reactions of the ketenes place them in a class by themselves. For example, they undergo auto-oxidation, and unite with certain tertiary bases such as quinoline and pyridine to form peculiar compounds known as "ketene bases."

Another reaction typical of the ketenes is their power of combining with various unsaturated substances to give addition compounds. This process usually results in the formation of a four-membered ring, one molecule of ketene combining with one molecule of the unsaturated substance:

$$\begin{array}{c} R_2C{=}CO \\ + \\ R_1{=}R_2 \end{array} \longrightarrow \begin{array}{c} R_2C\text{—}CO \\ \vert \quad\;\; \vert \\ R_1\text{—}R_2 \end{array}$$

The ease with which many ketenes polymerise may be traced to a similar cause. In this case derivatives of cyclobutane are generally produced:

$$2R_2C{=}CO \longrightarrow \begin{array}{c} R_2C\text{—}CO \\ \vert \quad\;\; \vert \\ OC\text{—}CR_2 \end{array}$$

[1] Schmidlin and Bergman, *Ber.*, 1910, 43, 2821. For the original method of preparation see Wilsmore, *J. C. S.*, 1907, 91, 1938.

Ketene, $CH_2{=}CO$ (preparation see above), is a colourless gas with an exceedingly unpleasant, pungent smell, reminiscent of both chlorine and acetic anhydride. Inhalation of the vapour causes severe headache. At $-56°$ it condenses to a colourless liquid which solidifies at $-151°$ to a white crystalline mass. The gas is readily soluble in ether. In the pure state ketene is very unstable and can only be preserved at a low temperature ($-80°$). At room temperature it polymerises slowly, and on strong heating decomposes into ethylene and carbon monoxide.

Methyl ketene, $(CH_3)CH{:}CO$, has so far only been obtained in ethereal solution. Even concentrated solutions are colourless, and these, when cooled in liquid air, solidify to a mass of colourless crystals. At a little above $-80°$ it polymerises spontaneously. Solutions of the ketene, even at high dilutions, soon assume a yellow or yellowish brown colour, probably owing to the formation of polymerisation products.

Dimethyl ketene, $(CH_3)_2C{:}CO$, is readily obtained in dilute ethereal or ethyl acetate solution by the action of zinc on bromo isobutyryl bromide. The pure ketene is a yellow liquid of unpleasant, choking smell, which boils at 34° to give a pale yellow gas. The solid substance, m.p. $-98°$, is also yellow in colour. Pure dimethyl ketene is very unstable and polymerises within a few hours to tetramethyl diketo cyclobutane.

THIO-ALDEHYDES AND THIO-KETONES

These compounds are produced by the action of hydrogen sulphide on aldehydes and ketones. They are liquids with a repulsive smell, and readily change by polymerisation into almost odourless compounds known as tri thio aldehydes or tri thio ketones. On oxidation with potassium permanganate they yield sulphones.

Thio acetaldehyde, ethanthial, $CH_3{\cdot}CH{:}S$, is a repulsively smelling oil, not known in the pure state, which on treatment with acids is readily converted into *tri thio aldehyde*, $(CH_3{\cdot}CHS)_3$. The latter occurs in two modifications melting at 101° and 125° respectively, both of which are odourless and may be oxidised to give the same *triethylidene trisulphone*, $C_6H_{12}(SO_2)_3$.

Tri thio acetone, $[(CH_3)_2CS]_3$, is obtained as the final product of the action of hydrogen sulphide on a mixture of acetone and concentrated hydrochloric acid. It melts at 24°, and on oxidation with permanganate yields *tri sulphone acetone*, $[(CH_3)_2C{:}SO_2]_3$.

X

Monobasic Carboxylic Acids

The characteristic group contained in all these acids is the carboxyl group $-C\begin{smallmatrix}\nearrow O \\ \searrow OH\end{smallmatrix}$, the hydrogen of which can be replaced by metals with the formation of salts. Consequently the basicity of the acids depends on the number of carboxyl groups present in the molecule. Those acids containing one such group are monobasic (monocarboxylic acids), and those possessing two such groups are dibasic (dicarboxylic acids), and so on, as illustrated by the following examples:—

CH_3COOH	$CH_2(COOH)_2$	$C_3H_5(COOH)_3$
Acetic acid (monobasic)	Malonic acid (dibasic)	Tricarballylic acid (tribasic)

The acids are called saturated or unsaturated according to the state of the hydrocarbon radicals attached to the carboxyl group Monobasic saturated acids of the aliphatic series are commonly known as **fatty acids**, since many of them are prepared from fats

Nomenclature—The names of the fatty acids all terminate in the syllable *-ic*, and generally indicate their source of preparation, as in formic acid (from ants), or the number of carbon atoms in the molecule, as in hexoic acid, $C_6H_{12}O_2$

According to the Geneva nomenclature the acids are named from the parent hydrocarbon by the addition of the word "acid," polybasic acids being further distinguished as di-, tri-, tetra-acids, and so on

The usual English and American practice is to employ the common names in describing saturated monobasic acids and their derivatives, the position of substituents being shown in the usual manner by the use of numbers or Greek letters (see p 100) Polybasic acids are frequently described as poly-carboxy hydrocarbons, and unsaturated linkings indicated by the endings -ene, -ine (see p 108), as in the following examples The Geneva nomenclature is also given in italics

$CH_3 \cdot CH_2 \cdot CH(CH_3) \cdot COOH$
α Methyl butyric acid or methyl-ethyl acetic acid
(2 *Methyl butane acid*)

$CH_3 \cdot CH : CH \cdot CH_2 \cdot CH_2 \cdot COOH$
γδ or Δ^4 hexenic acid
(4-*Hexene* 1 acid)

$HOOC \cdot CH_2 \cdot CH_2 \cdot CH : CH \cdot COOH$
Δ^{α}-Butene-αδ dicarboxylic acid
(2 *Hexene*-1 6 *diacid*)

In the discussion of reactions it is frequently necessary to refer to that group of atoms which remains when the hydroxyl group is removed from a fatty acid, such groups, which are not capable of existence in the free state, are known as "acyl" groups or acid radicals, and are named after the corresponding acid by adding the termination *yl* to a suitable contraction of the latter, *eg*

O	O	O	O
$H \cdot C$—	$H_3C \cdot C$—	$C_2H_5 \cdot C$—	$C_3H_7 \cdot C$—
Formyl	Acetyl	Propionyl	Butyryl

I—SATURATED MONOBASIC FATTY ACIDS, $C_nH_{2n+1}COOH$

Properties and Chemical Behaviour—The fatty acids of low carbon content are corrosive liquids of pungent smell which distil without decomposition, dissolve readily in water and are acid in reaction Those next in the series (C_4 to C_9) are oily compounds, sparingly soluble in water, and smelling unpleasantly of rancid butter or perspiration The members from C_{10} upwards are solids, which are no longer soluble in water but dissolve readily in alcohol and ether, they cannot be distilled without decomposition except under diminished pressure

As already mentioned, the hydrogen of the carboxyl group is replaceable by metals and also by alkyl groups In the latter case the esters formed have the same characteristic properties as those of the mineral acids (p 146)

Acids may also be converted into *acid chlorides* by exchanging the hydroxyl group for chlorine, or into *acid anhydrides* by exchanging the replaceable hydrogen of the carboxyl group by an acid radical,

$$\underset{\text{Acetyl chloride}}{CH_3\ CO\ Cl} + \underset{\text{Sodium acetate}}{CH_3\ CO\ ONa} = \underset{\text{Acetic anhydride}}{\begin{matrix} CH_3\ CO \\ CH_3\ CO \end{matrix}\!\!>\!O} + NaCl$$

On replacing the hydroxyl group by —SH we obtain *thio-acids*, by —NH_2 *acid amides*, and from the latter by removal of water the *nitriles*

$$\underset{\text{Thio acetic acid}}{CH_3\ CO\ SH} \qquad \underset{\text{Acetamide}}{CH_3\ CO\ NH_2} \qquad \underset{\text{Acetonitrile}}{CH_3\ C{\equiv}N}$$

Chloro- or bromo-substituted carboxylic acids may be prepared by the direct action of halogen on the acid

With the exception of formic acid the majority of the fatty acids are little affected by ordinary oxidising agents

On treatment with concentrated sulphuric acid the tertiary acids, in particular, undergo decomposition to give carbon monoxide and the corresponding carbinols [1]

Organic acids also react with hydrogen peroxide to yield per-acids, such as per-formic acid and per-acetic acid [2]

Other changes undergone by carboxylic acids have already been mentioned in previous chapters, compare pp 101, 103, 134, 160, 168

With regard to the catalytic action of finely divided metals, see Mailhe, *Ch Zeit*, **1919**, 242, 254

An important biological process is the *oxidation of fatty acids at the β-carbon atom* to give lower acids This was discovered by Knoop, who found that phenyl propionic acid introduced as food was eliminated in the urine as benzoic acid (in the form of hippuric acid), $C_6H_5\ CH_2\ CH_2\ COOH \longrightarrow C_6H_5\ COOH$ In diabetic patients butyric acid becomes transformed into β-hydroxy-butyric acid $CH_3\ CH_2\ CH_2\ COOH \longrightarrow CH_3\ CHOH\ CH_2\ COOH$ By further oxidation the latter probably oxidises to the β-ketonic compound aceto-acetic acid, which readily decomposes into acetone and carbon dioxide (pp 178 and 256) $CH_3\ CO\ CH_2\ COOH \longrightarrow CH_3\ CO\ CH_3 + CO_2$ On the other hand, benzoic acid, $C_6H_5\ COOH$, and phenylacetic acid, $C_6H_5\ CH_2\ COOH$, in which β-oxidation cannot occur, are unchanged in the organism Dakin [3] and Neubauer have shown that ammonium salts of fatty acids can be disrupted at the β-position by purely chemical oxidation, using hydrogen peroxide or potassium persulphate

[1] A Bistrzycki *Ber*, 1907, 40, 4370, 1908, 41, 1665 [2] J d'Ans and W Frey, *Ber*, 1912, 45, 1845 [3] *Am Ch J*, 1910, 44, 41

Methods of Formation.—Of the numerous reactions available for this purpose only the most important are described here.

Saturated monobasic acids are produced:

1. By oxidation of the corresponding primary alcohol or aldehyde (pp. 130 and 166).

2. By allowing alkyl iodides to react with potassium cyanide, and hydrolysing the alkyl cyanide or nitrile so formed.

$$\underset{\substack{\text{Methyl cyanide}\\\text{(Aceto nitrile)}}}{CH_3.C{:}N} + 2H_2O = \underset{\text{Acetic acid}}{CH_3.CO_2H} + NH_3$$

In this reaction we may assume the intermediate formation of the compound $CH_3.C(OH)_3$ with three hydroxyl groups attached to the same carbon atom. Such compounds are not stable (p. 130) and immediately lose a molecule of water to yield carboxylic acids. These hypothetical compounds have been termed ortho acids and give quite stable esters, *e.g.* *ortho formic ester*, $H.C(OC_2H_5)_3$.

3. By Wanklyn's reaction, which is of theoretical importance as affording a simple means of passing from the metallo-organic compounds to the acids. It consists in the action of carbon dioxide on sodium alkyls,

$$\underset{\text{Sodium methyl}}{CH_3.Na} + CO_2 = \underset{\text{Sodium acetate}}{CH_3.CO.ONa}$$

The interest of this reaction lies in its simplicity. Unfortunately the alkyl derivatives of alkali metals are unstable and difficult to prepare, so that the method is of little practical value.

4. Carboxylic acids have recently been synthesised in an analogous manner by Grignard, by treating magnesium alkyl halides in ethereal solution with carbon dioxide and decomposing the additive compound so formed with dilute sulphuric acid.

$$R.Mg.X + CO_2 = RCO.O.MgX$$
$$R.CO.OMgX + H_2O = R.CO.OH + HO.MgX$$

5. By the action of carbon monoxide on alcoholates at high temperatures, *e.g.*,

$$CH_3.ONa + CO = CH_3.COONa$$

6. The hydrolysis of acetoacetic ester and its derivatives is a useful method for the preparation of monocarboxylic acids. This is described in detail later.

7. On the technical scale the higher fatty acids are prepared by the hydrolysis of fats.

8. In the animal organism fatty acids are converted into lower acids by oxidation at the β-carbon atom (see previous page).

9. Lower fatty acids are also formed by the reductive degradation of amino-acids.[1]

[1] C. Neuberg and Rosenberg, *Biochem. Zeitschr.*, 1907, 7, 199. Neuberg, *ibid.*, 1911, 37, 490.

Isomerism.—The number of structural isomerides theoretically possible for a carboxylic acid of given carbon content is the same as that for the corresponding aldehyde or primary alcohol, since the isomerism depends on the different arrangement of the carbon atoms in the hydrocarbon radical united to the carboxyl group. Among the first three members of the series, therefore, no isomerism is possible. The fourth, however, exists in two isomeric forms.

Formic acid, *methane acid*, *acidum formicum*, H.COOH, occurs in ants, stinging nettles and many liquids of animal origin, such as perspiration and urine; it is obtainable from any of these sources by distillation with water. It may be formed according to the general methods given above, but is usually prepared by one of the following special methods.

Formic acid was originally obtained from oxalic acid by heating it with glycerol at 100° to 110° (Berthelot). Under these conditions the oxalic acid decomposes with the formation of certain intermediate products to yield chiefly carbon dioxide and formic acid.[1]

$$\underset{\text{Oxalic acid}}{\begin{array}{l}COOH\\ |\\ COOH\end{array}} = CO_2 + H.COOH$$

Recently it has been manufactured by heating carbon monoxide with soda lime or sodium hydroxide. From the sodium formate thus produced, the pure anhydrous acid is prepared by distillation with sodium hydrogen sulphate.

$$CO + NaOH = H.COONa$$

From dilute solutions the anhydrous acid is isolated by treatment with litharge and decomposing the dried lead salt with hydrogen sulphide at 100°.

Anhydrous formic acid melts at 8.6°, boils at 100.6°, and has a penetrating pungent odour. It is strongly corrosive and raises blisters on the skin. With water, alcohol and ether it is miscible in all proportions. The acid gives rise to salts known as *formates*, all of which dissolve in water, although those of lead and silver are only sparingly soluble.

Owing to the presence of an aldehyde grouping in the molecule, formic acid $\left(HO-C\begin{smallmatrix}\diagup H\\ \diagdown\!\!\diagdown O\end{smallmatrix}\right)$ tends to undergo oxidation with the formation of carbon dioxide and water, and in this respect differs from all its homologues.

$$HCOOH + O = CO_2 + H_2O$$

Consequently it is a reducing agent, as is shown by its behaviour with

[1] See Chattaway, *J. C. S.*, 1914, **105**, 151.

silver and mercury salts When heated with formic acid in aqueous solution the former yield a silver mirror and the latter mercurous salts

Above 160° formic acid decomposes into carbon dioxide and hydrogen The same reaction takes place at ordinary temperature under the catalytic influence of finely divided rhodium, iridium, or ruthenium, and less readily with spongy platinum From this it may be concluded that the molecule has a tendency to split off molecular hydrogen according to the equation $H \cdot COOH = CO_2 + H_2$ The reduction of formic acid by the addition of hydrogen would therefore be expected to present special difficulty, and in actual fact, even under the most diverse experimental conditions, it is only possible to obtain minute yields of formaldehyde or methyl alcohol by the reduction of formic acid or its salts with hydrogen It should be noted, however, that good yields of formaldehyde or methyl alcohol may be obtained by auto-reduction,[1] by heating the acid with a suitable contact agent

When formic acid is warmed with concentrated sulphuric acid it decomposes smoothly into pure carbon monoxide and water

$$HCOOH = H_2O + CO$$

Acetic Acid, *Ethane Acid*, *Acidum aceticum*, $CH_3 \cdot COOH$

Salts of acetic acid are found in the sap of many plants and also in perspiration From the practical standpoint the acid is one of the most important of the organic acids, and is prepared technically by the oxidation of dilute ethyl alcohol (wine, beer, etc), by the dry distillation of wood and more recently from acetylene as starting material

I In the preparation of dilute acetic acid or *vinegar* from liquids containing alcohol, the oxidation is brought about by the action of air under the influence of bacteria, chiefly *Bacterium aceti* This acetic fermentation[2] occurs during the souring of beer or wines and leads to the formation of white or wine vinegar Fermented liquids containing a small proportion of alcohol are utilised in this preparation A more modern method known as the *quick vinegar process* is conducted in the following manner

Large wooden vats are filled with basket-work or beech shavings moistened with strong vinegar containing acetic bacteria The basket-work serves on the one hand to present a large surface of liquid to the oxidising action of the air, and on the other provides a suitable medium for the growth of the bacteria The tubs are fitted with a perforated cover and the alcoholic liquid is run in and allowed to trickle slowly over the shavings Air enters through holes in the lower walls of the vessel and passes upward in the opposite direction to the flow of the

[1] K A Hofmann and Schibsted, *Ber*, 1918, 51, 1389, 1398 For the catalytic decomposition of free formic acid, see Sabatier and Mailhe, *C*, 1911, II, 15 [2] For detailed information concerning acetic fermentation, see Buchner and Gaunt, *Ann*, 1906, 349, 140

liquid. Oxidation is completed by repeating the process several times, the temperature being maintained at 30° to 35°. The whole reaction lasts about fourteen days and yields a table vinegar with about 6 to 7 per cent. of acetic acid.

II. Stronger acetic acid is prepared by the dry distillation of wood (see p. 135). The liquid products of distillation separate into a lower layer of wood tar and an upper aqueous layer known as pyroligneous acid. The chief constituents of the latter, apart from water, are acetic acid (10 per cent.), methyl alcohol (1 to 2 per cent.) and acetone (0.5 per cent.). After the removal of tar, the crude pyroligneous acid is distilled from a copper vessel and the distillate trapped in milk of lime, by which means acetic acid and its homologues are retained as calcium salts. Methyl alcohol and acetone, being volatile, pass on and are condensed in a special apparatus. The raw acetate of lime is freed from tarry matter and dried, when it constitutes the "grey acetate" of commerce (containing 80 per cent. of calcium acetate), from which crude 70 to 75 per cent. acetic acid is generally prepared by direct distillation with sulphuric acid. In another process the crude acetate is converted into sodium acetate by treatment with sodium sulphate. Sodium acetate crystallises exceptionally well and is thus readily freed from the accompanying salts of homologous acids (such as propionic and butyric acids). After heating the sodium acetate so obtained to remove water it is treated with concentrated sulphuric acid, and pure acetic acid distilled over. The pure acid solidifies on cooling and comes on to the market under the name of *glacial acetic acid*. The manufacture of glacial acetic acid from sodium acetate is now rarely carried out, as it is almost exclusively prepared by rectification of the 70 to 75 per cent. acid obtained from "grey" acetate of lime. In this case sulphurous acid and dilute acetic acid distil over first, followed by glacial acetic acid and finally propionic and butyric acids.

III. It has long been known that water combines with acetylene under the influence of mercury salts to form acetaldehyde, which on oxidation may be converted into acetic acid. The development of this reaction has recently led to the manufacture of acetic acid from calcium carbide.

Properties.—Anhydrous acetic acid melts at 16.6° to a corrosive liquid of pungent smell, which boils at 118°. In contact with the skin it produces painful wounds. It is specifically heavier than water, with which it mixes in all proportions, solution being accompanied by liberation of heat and contraction in volume. On adding water to acetic acid the specific gravity first rises, but falls on further dilution. Hence it is not possible to ascertain the strength of an aqueous mixture from specific gravity data alone. The acid is hygroscopic, and stable towards oxidising agents such as chromic acid and potassium permanganate. Since it is an excellent solvent for many organic compounds

it is frequently employed as such in chromic acid oxidations Pure acetic acid should not decolorise one drop of a solution of potassium permanganate

Acetic acid gives rise to salts known as *acetates*, most of which are soluble in water *Silver acetate* is only sparingly soluble The following are of technical importance *sodium acetate*, $NaC_2H_3O_2+3H_2O$, used for artificial cooling, *lead acetate* or *sugar of lead*, $Pb(C_2H_3O_2)_2+3H_2O$, and *basic acetate of lead*, $Pb(OH)(C_2H_3O_2)$, used in the manufacture of lead preparations (e g, *white lead*)

Acetates of aluminium, chromium, iron and *copper* are largely employed as mordants in dyeing and printing

Propionic acid, *methyl acetic acid*, CH_3 CH_2 COOH, may be prepared by the oxidation of normal propyl alcohol or by the hydrolysis of ethyl cyanide It is a liquid of b p 141°, which resembles acetic acid Propionic acid is thrown out of its aqueous solution in the form of an oil by the addition of salts

Butyric Acids, C_3H_7 COOH

Two structural isomerides of this acid are possible

1 **Normal butyric acid**, *fermentation butyric acid, ethyl-acetic acid, butane-acid*, CH_3 CH_2 CH_2 COOH, occurs as the glyceryl ester (*butyrin*) in butter, and is also found in the free state in perspiration

It is formed by the general methods available for the preparation of fatty acids, and is known as fermentation butyric acid owing to its production under certain conditions during the fermentation of sugar, starch or lactic acid [1] It is a viscous, unpleasant-smelling liquid, b p 163°

2 **Isobutyric acid**, *dimethyl-acetic acid, methyl-propane acid*, $(CH_3)_2CH$ COOH, boils at 154° It resembles butyric acid in its properties, but is more easily oxidised The calcium salt differs from that of normal butyric acid in being more soluble in hot water than in cold

Valeric Acids, C_4H_9 COOH

Four structural isomerides are possible, all of which are known, viz —

Normal valeric acid, CH_3 CH_2 CH_2 CH_2 COOH, b p 185°
Isovaleric acid, $(CH_3)_2CH$ CH_2 COOH, b p 175°
Methyl ethyl acetic acid, $(CH_3)(C_2H_5)CH$ COOH, b p 177°
Trimethyl acetic acid, $(CH_3)_3C$ COOH, b p 164°

Isovaleric acid, *ordinary valeric acid, 3-methyl-butane acid*, $(CH_3)_2CH$ CH_2 COOH, occurs in the free state in many plants, particularly in valerian root, from which it is prepared by boiling with aqueous sodium carbonate The product so obtained is the ordinary valeric acid, *Acidum valerianicum*, of pharmacy, and contains also some optically active methyl-ethyl acetic acid A similar mixture is obtained by the oxidation of fermentation amyl alcohol with chromic acid

[1] For the chemical changes which take place during the butyric fermentation, see E Buchner and J Meisenheimer, *Ber*, 1908, **41**, 1410 Neuberg and Arinstein, *C*, 1921, III, 1091

Higher Fatty Acids, Oils, Fats, Waxes[1] and Soaps

Of the higher fatty acids, the normal members of the series with an even number of carbon atoms are found as esters in oils and fats of vegetable and animal origin. The most noteworthy of these are *palmitic acid*, $C_{16}H_{32}O_2$, melting at 62°, and *stearic acid*, $C_{18}H_{36}O_2$, melting at 69°. In frequent association with these two compounds are certain unsaturated acids, such as the liquid *oleic acid*, $C_{18}H_{34}O_2$. Oils and fats consist mainly of mixtures of the neutral glyceryl esters of these three acids, formed, as illustrated in the following equation, by the combination of the trihydric alcohol glycerol with three molecules of monobasic acid.

$$\underset{\text{Glycerol}}{\begin{array}{l} CH_2\cdot OH \\ | \\ CH\cdot OH \\ | \\ CH_2\cdot OH \end{array}} + \underset{\text{Palmitic acid}}{3C_{15}H_{31}\cdot COOH} = \underset{\substack{\text{Palmitin} \\ \text{(Glyceryl tripalmitate)}}}{\begin{array}{l} CH_2\cdot O\cdot CO\cdot C_{15}H_{31} \\ | \\ CH\cdot O\cdot CO\cdot C_{15}H_{31} \\ | \\ CH_2\cdot O\cdot CO\cdot C_{15}H_{31} \end{array}} + 3H_2O$$

Waxes differ chemically from fats in being fatty acid esters, not of glycerol, but of higher monohydric alcohols of the methyl alcohol series, such as cetyl alcohol, $C_{16}H_{33}OH$ (in *spermaceti*) and myricyl alcohol, $C_{30}H_{61}OH$ (in *beeswax*). In addition they also contain higher alcohols and acids in the uncombined state.

Of the glyceryl esters of the three acids named above, known as palmitin, stearin and olein respectively, the last has a considerably lower melting-point than the others.

Palmitin	$C_3H_5(O\cdot CO\cdot C_{15}H_{31})_3$	m.p. 63°
Stearin	$C_3H_5(O\cdot CO\cdot C_{17}H_{35})_3$	„ 65.5°
Olein	$C_3H_5(O\cdot CO\cdot C_{17}H_{33})_3$	„ −6°

It follows, therefore, that the melting-point of a fat or oil, and its consistency at the ordinary temperature, depend very largely on the relative proportions of the glycerides present.

These oils and fats are obtained only from animal and vegetable sources. In plants they function like starch as food reserves, and for this purpose they are accumulated in the seeds and tubers. Animals also use vegetable oils and fats as food, employing them to build up new fats, which are deposited in the body and if required are available as reserves in time of hunger.

Oils and fats are prepared from naturally occurring products by expressing, melting or boiling out, or by extraction with solvents. Those intended for table use are generally expressed or melted out. When intended for other purposes all four processes may come into operation. Frequently the melting-out process is performed under pressure.

Fats are insoluble in water, and only sparingly soluble in alcohol;

[1] See J. Lewkowitsch, *Chemical Technology and Analysis of Oils, Fats and Waxes*.

they dissolve readily in ether, carbon disulphide, benzine, chloroform and similar solvents.

On heating with alkalis (lime, magnesia, etc.), mineral acids, or with water at high temperature and pressure, fats are hydrolysed to form glycerol and fatty acids :—

$$
\begin{array}{l}
CH_2 \cdot O \cdot C_{15}H_{31} \\
| \\
CH \cdot O \cdot CO \cdot C_{15}H_{31} \\
| \\
CH_2 \cdot O \cdot CO \cdot C_{15}H_{31} \\
\text{Palmitin}
\end{array}
+ 3H_2O = \underset{\text{Palmitic acid}}{3C_{15}H_{31} \cdot COOH} +
\begin{array}{l}
CH_2 \cdot OH \\
| \\
CH \cdot OH \\
| \\
CH_2 \cdot OH \\
\text{Glycerol}
\end{array}
$$

This hydrolysis is brought about by the use of alkalis in the manufacture of soaps, which are alkali salts of the fatty acids. Hence the above reaction is sometimes termed *saponification* (p. 147).

Hydrolysis may also be effected at relatively low temperatures (below 40°) by the action of the fat-hydrolysing enzyme *lipase* on an aqueous emulsion of the fat. Ferments of this type are present in the digestive organs and also in plants.[1]

The **free fatty acids** required for the production of candles, and glycerol, which is utilised nowadays for a great many purposes, are usually prepared by hydrolysing fats with sulphuric acid, or with water alone under high pressure (15 to 16 atmospheres) and temperature (*ca.* 200°). The raw materials most frequently employed are tallow, lard, cocoanut oil and palm oil.

As obtained by this process the mixture of fatty acids forms a semi-solid mass at ordinary temperatures, since it contains liquid oleic acid in addition to solid palmitic and stearic acids. Oleic acid is removed under pressure and used for the manufacture of soap. After admixture with a little wax to prevent crystallisation the solid acids are used in the production of "stearine" candles.

It has already been stated that **soaps** are the salts and particularly the alkali salts, of palmitic, stearic and oleic acids. They are prepared by saponifying fats by boiling with caustic soda or potash. The reaction with palmitin, a fat very widely distributed in nature, is expressed by the equation :—

$$
\begin{array}{l}
CH_2 \cdot O \cdot CO \cdot C_{15}H_{31} \\
| \\
CH \cdot O \cdot CO \cdot C_{15}H_{31} \\
| \\
CH_2O \cdot CO \cdot C_{15}H_{31} \\
\text{Palmitin}
\end{array}
+ 3NaOH = \underset{\substack{\text{Sodium palmitate} \\ \text{(a soap)}}}{3C_{15}H_{31} \cdot COONa} +
\begin{array}{l}
CH_2 \cdot OH \\
| \\
CH \cdot OH \\
| \\
CH_2 \cdot OH \\
\text{Glycerol}
\end{array}
$$

[1] An industrial process for converting fats into fatty acids and glycerol depends on the action of an enzyme occurring in the castor bean. After removing the oil present in the beans the residue is ground up with the fat and mixed with a dilute (*e.g.* 1/10 normal) solution of sulphuric acid, when an emulsion is formed. At a temperature of 30° to 40° the fatty acids separate out in the pure state during the space of two or three days, while glycerol collects in the solution to the extent of 30 to 40 per cent. See Hoyer, *Ber.*, 1902, 35, 3988; 1904, 37, 1436; *C.*, 1905, II, 582; 1907, I, 646.

Hard soaps are sodium salts containing a preponderance of so[...] acids, *soft soaps*, on the other hand, are potassium salts with a hig[...] proportion of oleate. These soaps differ in solubility, and whe[...] potassium soaps are treated with excess of brine they are converted into the less soluble sodium soaps ("salting out" process)

$$\underset{\substack{\text{Potassium palmitate}\\\text{(soft soap)}}}{C_{15}H_{31}\cdot COOK} + NaCl = \underset{\substack{\text{Sodium palmitate}\\\text{(hard soap)}}}{C_{15}H_{31}\cdot COONa} + KCl$$

The following procedure is adopted in the manufacture of curd soap from tallow. The fat is first placed in a large cylindrical vessel and a dilute solution of caustic soda ("lye" of about 15° Bé.) introduced, amounting to about one quarter of the theoretical quantity. Steam is blown in and the mixture vigorously boiled. An emulsion is first formed, and as the alkali enters into reaction, additional amounts are run in slowly till finally an excess is present and the mass appears clear. The soap is thrown out of solution by the addition of salt and allowed to settle, after which the lower layer of liquid (sweet lye), containing the glycerol, is run off from below. The soap is then again boiled with water and alkali to complete the saponification.

The lye is once more run off and the soap boiled up with the requisite amount of water (hydration) and again allowed to settle. A dark coloured lye containing metallic soaps, chiefly of iron, separates out at this stage. The solid soap is finally removed, cut up and dried.

Sodium and potassium soaps dissolve in a small amount of water to give a clear solution, but in the presence of much water hydrolytic dissociation of the salt takes place with the formation of free acid and alkali. According to conditions the free acid may remain suspended in the liquid in the form of oily drops, or be precipitated in combination with the soap as a sparingly soluble acid salt. On the liberation of free alkali depends the cleansing action of soap. At this dilution the alkali loosens grease and dirt without attacking the skin or the material which is being cleaned. At the same time the precipitated salts envelop the particles of detached fat and dirt and prevent them from being again deposited on the fibres.

In addition to the water-soluble soaps of sodium and potassium, the term soap also includes insoluble and sparingly soluble salts of fatty acids, such as those of calcium, lead (lead plaster), zinc, aluminium, tin and others, many of which are used industrially.

Calcium soaps are so sparingly soluble that they are deposited on mixing sodium or potassium soaps with solutions of calcium salts.

$$2\underset{\text{Potassium palmitate}}{C_{15}H_{31}\cdot COOK} + CaCl_2 = \underset{\text{Calcium palmitate}}{(C_{15}H_{31}COO)_2Ca} + 2KCl$$

For this reason water containing lime salts gives no lather with soap, the lime soap separating out as a white flocculent precipitate. Such water is called "hard" and is difficult to use for washing purposes.

Lead plaster contains lead soaps and is usually obtained by heating soft fats (lard or oil) or oleic acid with litharge, till the product is easily

moulded by the warmth of the hand but solidifies on cooling The plaster still contains all the liberated glycerol and some unchanged fat *Soaps of lead* and *manganese* are also utilised in the preparation of varnishes

Among the still higher acids of this series are *arachic acid*, $C_{19}H_{39}COOH$ (present as the glyceride in earth-nut oil), *behenic acid*, $C_{21}H_{43}COOH$, *lignoceric acid*, $C_{23}H_{47}COOH$ (in earth nut oil and wood tar), *cerotic acid*, $C_{25}H_{51}COOH$ (as ester in beeswax), *melissic acid*, $C_{29}H_{59}COOH$ (in carnauba wax and beeswax)

Phosphatides—Closely related to the fats is a class of complex substances known as phosphatides (lipoids) which is of great physiological importance These compounds are glycerides in which the organic acid residues (in either the α- or β-positions in the glycerol molecule) are partially replaced by groups containing phosphoric acid and a base such as choline (p 239) or hydroxy-ethylamine (p 238) Phosphatides occur widely distributed in the animal and vegetable kingdoms, *e g*, in yolk of egg, brain and seeds Their constitution is deduced from their behaviour on hydrolysis with dilute acids or alkalis

One of the best known representatives is **lecithin** (apparently a mixture of closely related products) which decomposes into choline and *distearyl-glycerol-phosphoric acid* (I) On further hydrolysis the latter yields two molecules of stearic acid, one molecule of phosphoric acid and glycerol Lecithin (II) is therefore considered to be the choline ester of I Various *a-lecithins* are known differing from the above in the partial or complete replacement of the stearic groups by

$$
\begin{array}{lll}
\text{I} & & CH_2\text{—}O\cdot COC_{17}H_{35} \\
 & & | \\
 & (\beta) & CH\text{—}O\cdot COC_{17}H_{35} \\
 & & | \\
 & (\alpha) & CH_2\text{—}OPO(OH)_2
\end{array}
\qquad
\begin{array}{ll}
\text{II} & CH_2\text{—}O\cdot COC_{17}H_{35} \\
 & | \\
 & CH\text{—}O\cdot COC_{17}H_{35} \\
 & | \\
 & CH_2\text{—}OPO(OH)O\cdot CH_2\cdot CH_2\cdot N(CH_3)_3OH
\end{array}
$$

palmitic, oleic or similar acid residues *β-Lecithins* contain the phosphoric complex in the β-position Lecithins are very hygroscopic, unstable in air, and dissolve readily in alcohol and ether

Kephalin, which commonly accompanies lecithin in the crude state, is a phosphatide derived from hydroxy-ethylamine instead of choline It is separated from lecithin by means of its low solubility in alcohol

II —UNSATURATED MONOBASIC ACIDS

1 Oleic Acid Series, $C_nH_{2n-1}COOH$

The best known member of the class is oleic acid, from which the series takes its name These acids may be regarded as derivatives of the olefines C_nH_{2n}, and stand in the same relationship to the fatty acids as the olefines to the paraffins

They may be obtained by methods analogous to those given for the fatty acids, also by the general methods available for the preparation

of unsaturated compounds, *e g* by the removal of hydrogen halide from monohalogen substitution products of fatty acids (I), or of water from the corresponding monohydroxy acids (II)

$$\text{I} \quad \underset{\text{Chloro propionic acid}}{CH_2Cl\ CH_2\ COOH} \longrightarrow \underset{\text{Acrylic acid}}{CH_2\ CH\ COOH}$$

$$\text{II} \quad \underset{\text{Hydroxy-butyric acid}}{CH_3\ CHOH\ CH_2\ COOH} \longrightarrow \underset{\text{Crotonic acid}}{CH_3\ CH\ CH\ COOH}$$

In chemical and physical properties these compounds strongly resemble the fatty acids, but they differ from them in certain points, particularly in their *addition reactions* They combine with chlorine, bromine and iodine to form dihalogen derivatives, and with hydrogen halides to give monohalogen derivatives of the fatty acids In the latter case halogen usually attaches itself to the carbon atom further away from the carboxyl group

$$\underset{\text{Acrylic acid}}{CH_2\ CH\ COOH} + 2Cl = \underset{\text{Dichloropropionic acid}}{CH_2Cl\ CHCl\ COOH}$$

Unsaturated acids may be converted into the corresponding saturated compounds by catalytic reduction Thus when oleic acid is treated with hydrogen at ordinary temperatures in the presence of colloidal palladium it yields stearic acid Mixtures of glycerides of saturated and unsaturated aliphatic acids, such as are present in animal and vegetable fats, may also be treated in the same manner [1] Castor oil, olive oil and cod-liver oil, which are rich in unsaturated glycerides, can be practically completely reduced by this process and thereby transformed into a crystalline, tallow-like mass of high melting-point It is a matter of technical importance that other and cheaper catalysts, such as finely divided nickel, may be used in place of palladium for this purpose, and also that pure hydrogen may be replaced by the gaseous mixtures of hydrogen obtained as industrial by-products Under such treatment oils and soft fats generally yield a harder product which possesses many advantages, including a more pleasant taste and improved keeping qualities as compared with the starting material For this reason the *technical hardening of fats* is of great practical importance,[2] *e g* in the manufacture of margarine

Unsaturated acids unite with ozone to form unstable ozonides The ozonide of isocrotonic acid is a yellow, extremely explosive syrup, which decomposes energetically with water It evolves oxygen on standing and regenerates the original acid

Another characteristic of unsaturated acids is the ease with which they undergo *oxidation* (*cf* p 112) With mild oxidising agents the first step is the addition of two hydroxyl groups to yield a dihydroxy

[1] Paal and Roth, *Ber*, 1908, 41, 2282, 1909, 42, 1541 [2] See Crossley, *The Pharmaceutical Journal and Pharmacist*, 1914, 92, 637, 676 C Ellis, *J S C I*, 1912, 31, 1155, T Shaw, *ibid*, 1914, 33, 771

acid (III). On further oxidation, disruption occurs at the point originally occupied by the double bond and two molecules of saturated acids are formed (IV). In this manner it is possible to ascertain the position of the double bond in an unsaturated acid.

$$\text{III. } \underset{\text{Crotonic acid}}{CH_3 \cdot CH : CH \cdot COOH} + H_2O + O \longrightarrow CH_3 \cdot CHOH \cdot CHOH \cdot COOH$$

$$\text{IV. } CH_3 \cdot CHOH \cdot CHOH \cdot COOH + 3O \longrightarrow \underset{\text{Acetic acid}}{CH_3 \cdot COOH} + \underset{\text{Oxalic acid}}{COOH \cdot COOH} + H_2O$$

The molecule may also be disrupted by *fusion with sodium or potassium hydroxide* in the presence of air, saturated fatty acids being again produced:

$$\underset{\text{Crotonic acid}}{CH_3 \cdot CH : CH \cdot COOH} + O + H_2O \longrightarrow \underset{\text{Acetic acid}}{CH_3 \cdot CO_2H} + \underset{\text{Acetic acid}}{CH_3 \cdot CO_2H}$$

In this case, however, the chain does not always break at the point originally occupied by the double bond, since under the influence of alkalis the latter is frequently displaced towards the carboxyl group.[1] Fusion with alkali cannot therefore be employed to determine the position of the double bond.

Isomerism among the acids of the oleic series may be of two kinds: (1) *structural isomerism* caused by a different arrangement of the carbon atoms in the hydrocarbon chain, or a different position of the double bond, and (2) *geometrical isomerism* (see p. 48).

Acrylic acid, *propenoic acid*, $CH_2 : CH \cdot COOH$, is formed by oxidising acrolein with silver oxide, and is best prepared from glycol chlorohydrin as follows:

$$HO \cdot CH_2 \cdot CH_2Cl \longrightarrow HO \cdot CH_2 \cdot CH_2CN \longrightarrow CH_2 : CH \cdot COOH\text{[2]}$$

It melts at [illegible], boils at [illegible], and has a smell resembling that of acetic acid. It slowly polymerises on standing, and when reduced yields propionic acid.

Crotonic acid, $C_4H_6O_2$, is known in two stereo-isomeric forms, namely,

$$\underset{\text{[illegible]}}{\begin{array}{c} CH_3 \cdot C \cdot H \\ \| \\ H \cdot C \cdot COOH \end{array}} \qquad \underset{\text{[illegible]}}{\begin{array}{c} H \cdot C \cdot CH_3 \\ \| \\ H \cdot C \cdot COOH \end{array}} \qquad \begin{array}{c}\text{These acids are} \\ \text{also structurally} \\ \text{isomeric with}\end{array} \qquad \underset{\text{Methacrylic acid}}{\begin{array}{c} CH_3 \cdot C \cdot COOH \\ \| \\ CH_2 \end{array}} \qquad \underset{\text{Vinylacetic acid}}{\begin{array}{c} CH \cdot CH_2 \cdot COOH \\ \| \\ CH_2 \end{array}}$$

Ordinary or solid crotonic acid (m.p. [illegible], b.p. 180°) may be obtained by the general methods given above, or by oxidation of crotonic aldehyde. It is most readily prepared by heating malonic acid, $CH_2(COOH)_2$, with paraldehyde and acetic anhydride. On reduction with zinc and sulphuric acid it is converted into normal butyric acid, showing that it contains no branched chain. With nitric acid it breaks up, forming acetic acid and oxalic acid, whereas permanganate oxidises it to dihydroxy-butyric acid. When dissolved in toluene and irradiated with ultra-violet light it isomerises into isocrotonic acid.

[1] Fittig, *Ann.*, 1893, 283, 47, [illegible]. [2] J. H. N. van der Burg, *Rec. trav. chim.*, 1922, 41, 21. [3] K. v. Auwers and H. Wissebach, *Ber.*, 1923, 56, 715.

Iso or allocrotonic acid (m p 15°, b p 169°) may be prepared by reducing chloro isocrotonic acid with sodium amalgam and is very similar to the ordinary acid in properties On vigorous reduction it also yields normal butyric acid It is readily transformed into the isomeric acid, the change taking place to some extent merely on distillation A more complete transformation may be effected by heating at 170° to 180° in a sealed tube, or by the combined action of sunlight and traces of bromine on a solution of the acid in water or carbon disulphide Many similar examples of stereoisomeric change are met with in organic chemistry

Ozone reacts with an aqueous solution of isocrotonic acid, breaking up the molecule and forming acetaldehyde and glyoxalic acid From this reaction the constitution of the acid may be deduced

$$CH_3\ CH\ CH\ COOH + O_3 + H_2O = CH_3\ CHO + \underset{\text{Glyoxalic acid}}{O\ CH\ COOH} + H_2O_2$$

Meth acrylic acid, 2 *methyl 2 propene 1 acid* (m p 15°, b p 160 5°), occurs in oil of Roman camomile, *Anthemis nobilis*, and is formed from bromo isobutyric acid by elimination of HBr

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CBr\ COOH = \begin{matrix} CH_2 \\ CH_3 \end{matrix}\!\!>\!C\ COOH + HBr$$

On reduction meth-acrylic acid yields isobutyric acid It combines with bromine to give $\alpha\beta$ dibromo isobutyric acid, thus confirming the above constitutional formula

Vinyl acetic acid (b p 71° at 13 mm) has been obtained synthetically When boiled with caustic soda it is converted into ordinary crotonic acid and β hydroxy butyric acid

Oleic acid, $CH_3\ (CH_2)_7\ CH\ CH\ (CH_2)_7\ COOH$, is found as the glyceryl ester, *triolein*, especially in the fatty oils (such as almond oil or olive oil), from which it is obtained as a by-product after hydrolysis in the manufacture of stearic acid (see p 190) By taking advantage of the solubility of the lead salt in ether it may be separated from stearic and palmitic acids At ordinary temperatures it is a colourless, almost odourless and tasteless liquid At 4° it solidifies to a mass of colourless needles, which melt again when the temperature is raised to 14° In contact with air, however, it rapidly becomes yellow owing to oxidation, and acquires a sour, rancid smell Oleic acid gives stearic acid on reduction and dibromostearic acid on treatment with bromine, hence like stearic acid it contains a normal straight chain of carbon atoms Further, the double bond must be situated in the middle of the molecule, since careful oxidation leads to the formation of a mixture of *pelargonic acid*, $C_8H_{17}\ COOH$, and *azelaic acid*, $HOOC(CH_2)_7COOH$

Nitrous acid converts oleic acid into a solid compound, **elaidic acid**, m p 51° This possesses the same structure as oleic acid, with which it is stereoisomeric The relationship between oleic and elaidic acids is thus similar to that existing between the two crotonic acids Oleic acid is the *cis*- and elaidic acid the *trans*-form [1]

Proof of the stereoisomerism of oleic and elaidic acids is based

[1] J Boeseken and A H Belinfante, *Rec trav chim*, 1926, 45, 914 C Paal and H Schiedewitz, *Ber*, 1927, 60, 1221

on the observation that the dibromides of both these acids can be converted into the same *stearolic acid*, $C_8H_{17}C:C(CH_2)_7COOH$. Additional confirmation is found in the manner in which the ozonides of the two acids are decomposed by water.[1]

$$\underset{\text{Ozonide of oleic or elaidic acid}}{CH_3(CH_2)_7\underset{\diagdown\; O_3 \;\diagup}{CH-CH}(CH_2)_7CO_2H} + H_2O =$$

$$\underset{\text{Nonyl aldehyde}}{CH_3(CH_2)_7CH:O} + \underset{\text{Half aldehyde of azelaic acid}}{O:CH(CH_2)_7COOH} + H_2O_2$$

In the presence of air the half aldehyde of azelaic acid is rapidly oxidised to azelaic acid.

Oleic acid is used in the manufacture of soap.

Petroselic acid, $CH_3(CH_2)_{10}CH:CH(CH_2)_4COOH$, m.p. 33° to 34°, is obtained by the hydrolysis of a fat isolated from oil of parsley seeds.[2] With small amounts of nitrous acid it yields a stereoisomeric acid melting at 54°.

Glutaconic acid, $HOOC\cdot CH_2\cdot CH:CH\cdot COOH$, exhibits an interesting type of isomerism (see p. 66).

Among acids containing two double bonds in the molecule the most important are linoleic and sorbic acids.

Linoleic acid, $CH_3(CH_2)_4CH:CH\cdot CH_2\cdot CH:CH(CH_2)_7COOH$, b.p. 229° under 16 mm. pressure, occurs as the glyceride in linseed oil, hemp oil, poppy seed oil, and other drying oils. On reduction with hydriodic acid and phosphorus it yields stearic acid. In air it rapidly absorbs oxygen to form a hard resinous product.

Sorbic acid, $CH_3\cdot CH:CH\cdot CH:CH\cdot COOH$, m.p. 134·6°, is found in the unripe berries of the mountain ash. It may be prepared synthetically by warming croton aldehyde with malonic acid in the presence of pyridine as condensing agent.

$$\underset{\text{Crotonic aldehyde}}{CH_3\cdot CH:CH\cdot CHO} + \underset{\text{Malonic acid}}{H_2C(COOH)_2} = \underset{\text{Sorbic acid}}{CH_3\cdot CH:CH\cdot CH:CH\cdot COOH} + CO_2 + H_2O$$

Geranic acid, $(CH_3)_2C:CH\cdot CH_2\cdot CH_2\cdot C(CH_3):CH\cdot COOH$, may be obtained by the oxidation of citral (p. 178).

2. Acids containing an Acetylene Bond. Propiolic Acid Series, $C_nH_{2n-3}\cdot COOH$

These acids may be considered to be derivatives of the acetylene hydrocarbons, and are formed from acids of the oleic series in the same manner as the acetylenes are formed from the olefines, *i.e.* by the addition of halogen and subsequent removal of 2 mols. of hydrogen halide.

$$\underset{\text{Crotonic acid}}{CH_3\cdot CH:CH\cdot COOH} \to \underset{\text{Dibromobutyric acid}}{CH_3\cdot CHBr\cdot CHBr\cdot COOH} \to \underset{\text{Tetrolic acid}}{CH_3\cdot C:C\cdot COOH}$$

[1] Harries and Thieme, *Ann.*, 1905, 348, 311. [2] Vongerichten and Köhler, *Ber.*, 1909, 42, 1638.

They are also produced by the action of carbon dioxide on sodium derivatives of the acetylene hydrocarbons

$$CH \equiv CNa + CO_2 = CH \equiv C \cdot COONa$$

Like the acetylene hydrocarbons, these acids possess additive properties, and yield explosive compounds with ammoniacal solutions of silver and copper

Propiolic acid, *propargylic acid*, propine acid, $CH \equiv C \cdot COOH$ (m p 9°, b p 144°), corresponds to propargyl alcohol It has a smell resembling that of acetic acid and polymerises in sunlight to form a benzene derivative, *trimesic acid*, $C_6H_3(COOH)_3$ On reduction, propiolic acid is converted into propionic acid

Among other acids may be mentioned *tetrolic acid*, $CH_3 \cdot C \equiv C \cdot COOH$, m p 203°, and *octinic acid*, $CH_3(CH_2)_4C \equiv C \cdot COOH$ The methyl ester of the latter is employed as an artificial violet perfume

XI

Derivatives of Monocarboxylic Acids

I—DERIVATIVES FORMED BY SUBSTITUTION IN THE CARBOXYL GROUP

1 Esters

Methods of Formation—In properties and methods of formation the esters of monocarboxylic acids resemble the esters of the mineral acids (see p 146)

Thus they may be prepared by the direct interaction of acid and alcohol, a reversible reaction which proceeds towards equilibrium (p 147)

$$CH_3 \cdot COOH + C_2H_5OH \rightleftarrows CH_3 \cdot COOC_2H_5 + H_2O$$

In the preparation of the ester by this method the backward hydrolytic action of the water is reduced to a minimum by the addition of sulphuric acid or gaseous hydrochloric acid [1]

Sabatier and Mailhe have recently succeeded in preparing esters catalytically by the direct action of acids on alcohols in the presence of metallic oxides [2] At 280° to 300° the esterification proceeds quickly and smoothly, provided the catalyst brings about no marked decomposition of the acid When, for example, equimolecular amounts of a primary alcohol and an aliphatic acid are passed, in the form of vapour, over titanium oxide at 280° to 290°, a considerable amount of ester is produced

Other methods of preparing esters have already been mentioned on

[1] E Fischer, *Ber*, 1895, 28, 3252 Inorganic dehydrating salts may also be used for esterification [2] Sabatier and Mailhe, *C*, 1911, I, 1196

pp 121 and 147, and only the corresponding equations for the formation of ethyl acetate need be given here

$$CH_3 \cdot COOAg + C_2H_5I = CH_3 \cdot COOC_2H_5 + AgI$$

Silver acetate — Ethyl acetate

$$CH_3 \cdot CO \cdot Cl + C_2H_5OH = CH_3 \cdot COOC_2H_5 + HCl$$

Acetyl chloride

$$\begin{matrix} CH_3 \cdot CO \\ CH_3 \cdot CO \end{matrix}\!\!>\!O + C_2H_5OH = CH_3 \cdot COOC_2H_5 + CH_3COOH$$

Acetic anhydride

Methyl esters of carboxylic acids are also obtained by the action of dimethyl sulphate on the alkali salts of these acids.[1] The reaction takes place according to the following equation, a salt of methyl sulphuric

$$R \cdot COOK + (CH_3)_2SO_4 = R \cdot COOCH_3 + CH_3KSO_4$$

acid also being formed Better yields appear to be given by the use of salts in the solid state than in solution, it is also preferable to use potassium rather than sodium compounds

Properties—The esters of lower molecular weight are colourless liquids with a pleasant fruity odour Many of them are therefore prepared on a large scale in industry for use as artificial fruit essences They are generally insoluble in water, but soluble in alcohol and ether The boiling-point of an ester with a simple alkyl group (CH_3, C_2H_5, C_3H_7) is lower than that of the corresponding acid, but with the entrance of larger alkyl groups the position is reversed

When esters are superheated with water, or boiled with alkalis or mineral acids, they are decomposed into the component acids and alcohols (see *saponification* and *hydrolysis*, p 147)

$$CH_3 \cdot COOC_2H_5 + H_2O = CH_3 \cdot COOH + C_2H_5OH$$
$$CH_3 \cdot COOC_2H_5 + KOH = CH_3 \cdot COOK + C_2H_5OH$$

Owing to the ease with which the alkoxy group, $\cdot OR$, can be replaced by other groups, esters are very reactive compounds Thus on treatment with ammonia they are converted into acid amides, and with phosphorus pentachloride into acid chlorides (see below)

When an ethyl ester is warmed with methyl alcohol and a catalyst (*e g* CH_3ONa or HCl) a reversible change occurs and the corresponding methyl ester is formed Other esters and alcohols behave in the same manner This is known as **alcoholysis**

For reactions of esters with organo-magnesium halides, see p 134

Ethyl formate, $H \cdot CO \cdot OC_2H_5$, b p 55°, is used for flavouring artificial rum or arrak

Ethyl orthoformate, $CH(OC_2H_5)_3$, b p 146°, is obtained when chloroform is heated with sodium ethoxide in alcoholic solution,

$$CHCl_3 + 3Na \cdot OC_2H_5 = CH(OC_2H_5)_3 + 3NaCl$$

and is frequently used for synthetic purposes

[1] *Ber*, 1904, 37, 3658, 4036, 4144, Graebe, *Ann*, 1905, 340, 244

Ethyl acetate, acetic ester, $CH_3 \cdot CO \cdot OC_2H_5$, b p 78°, is manufactured in large quantities from alcohol, sulphuric acid, and acetic acid or sodium acetate It is used in the preparation of fruit essences and as a solvent in the manufacture of smokeless powder On account of its refreshing perfume it is also employed in medicine

Isoamyl acetate, amyl acetate, $CH_3 \cdot CO \cdot OC_5H_{11}$, b p 138°, is used as artificial pear essence, and also as fuel in the Hefner standard lamp

Ethyl butyrate is used as pineapple essence

Ethyl isovalerate and *isoamyl isovalerate* are employed as apple flavourings

It has already been explained on p 189 *et seq*, that fats and waxes are for the most part esters of higher fatty acids

2 Acid Chlorides

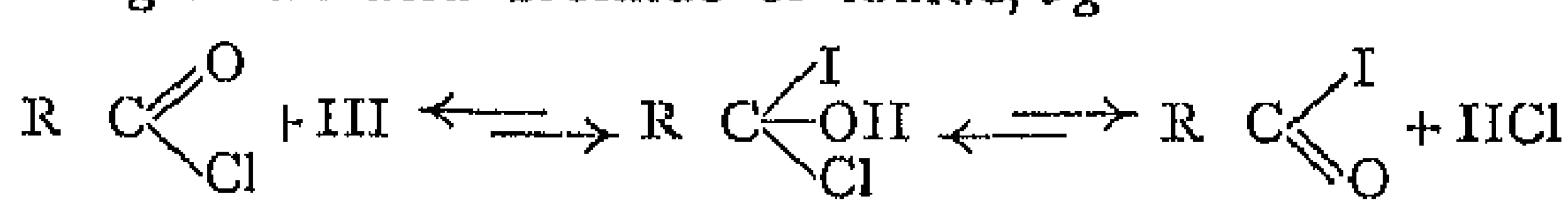
Acid chlorides are compounds formed by replacing the hydroxyl of an acid with chlorine, and therefore contain the group —CO Cl

This change can be brought about by the same reactions as are used for the replacement of the hydroxyl group in alcohols, see p 119 Acid chlorides may be prepared by the action of phosphorus trichloride or pentachloride on the acid or its alkali salts In many cases it is more satisfactory to use thionyl chloride, when the only by-products are sulphur dioxide and hydrogen chloride, both of which are gases

$$\underset{\text{Acetic acid}}{CH_3 \cdot COOH} + PCl_5 = \underset{\text{Acetyl chloride}}{CH_3 \cdot CO \cdot Cl} + POCl_3 + HCl$$

$$R \cdot COOH + SOCl_2 = R \cdot COCl + SO_2 + HCl$$

An excess of hydrogen bromide or iodide reacts with an acid chloride to give an acid bromide or iodide, *e g*



Properties—The lower acid chlorides are colourless liquids with a sharp, irritating smell Those of higher molecular weight are colourless crystalline compounds They boil at a lower temperature than the corresponding acids, and generally without decomposition In air they fume strongly, interacting with moisture to form the corresponding carboxylic acid and hydrochloric acid

$$CH_3 \cdot CO \cdot Cl + H_2O = CH_3 \cdot CO \cdot OH + HCl$$

With alcohols and phenols they interact with the production of esters

$$CH_3 \cdot CO \cdot Cl + H \cdot OC_2H_5 = CH_3 \cdot CO \cdot OC_2H_5 + HCl$$

For this reason acid chlorides, and especially *acetyl chloride* and *benzoyl chloride*, are frequently used for *detecting the presence of hydroxyl groups* in organic compounds

They also very readily interact with ammonia and primary and secondary amines (see p 162)

For their behaviour towards zinc alkyls and magnesium alkyl halides, see pp 134, 168

Acetyl chloride, $CH_3 \cdot CO \cdot Cl$, b p 55°, is prepared by the action of phosphorus trichloride on acetic acid It is a colourless mobile liquid of pungent smell

Acetyl nitrate, $CH_3 \cdot CO \cdot O \cdot NO_2$, may be obtained by the action of nitric anhydride on acetic anhydride It has been found to be a very energetic agent for the nitration of aromatic compounds[1]

3 Acid Anhydrides

These are prepared by the action of acid chlorides on the alkali salts of the acids

$$CH_3 \cdot CO \cdot Cl + CH_3 \cdot CO \cdot ONa = \begin{matrix} CH_3 \cdot CO \\ CH_3 \cdot CO \end{matrix}\!\!>\!O + NaCl$$

Acetic anhydride

Acid anhydrides are liquid or solid compounds of neutral reaction, which boil at a higher temperature than the corresponding acids They possess an unpleasant, pungent smell, and dissolve unchanged in indifferent organic solvents

In their chemical behaviour towards water, alcohols, phenols and bases, the acid anhydrides resemble acid chlorides, except that they react far less energetically

Acetic anhydride, $(CH_3 \cdot CO)_2O$, is a colourless liquid, b p 137° It is heavier than water and has a smell similar to that of acetic acid Like acetyl chloride it is a reagent of great value for introducing acetyl groups into alcohols, phenols, and primary and secondary amines

4 Thio acids, R CO . SH

Thio acids correspond to the thio alcohols or mercaptans (see p. 151), and are obtained by the action of phosphorus pentasulphide on acids, or by double decomposition between acid chlorides and potassium hydrosulphide They are liquids of nauseous odour

$$5CH_3 \cdot COOH + P_2S_5 = 5CH_3 \cdot CO \cdot SH + P_2O_5$$
$$CH_3 \cdot CO \cdot Cl + KSH = CH_3 \cdot CO \cdot SH + KCl$$

Thio acetic acid

Thio acetic acid, ethane thiolic acid, $CH_3 \cdot CO \cdot SH$, is a colourless liquid boiling below 100° It smells of acetic acid and hydrogen sulphide, and may be used for the acetylation of amines[2]

5 Carbithionic Acids, R CS SH

These compounds are produced by the action of carbon disulphide on organo magnesium halides

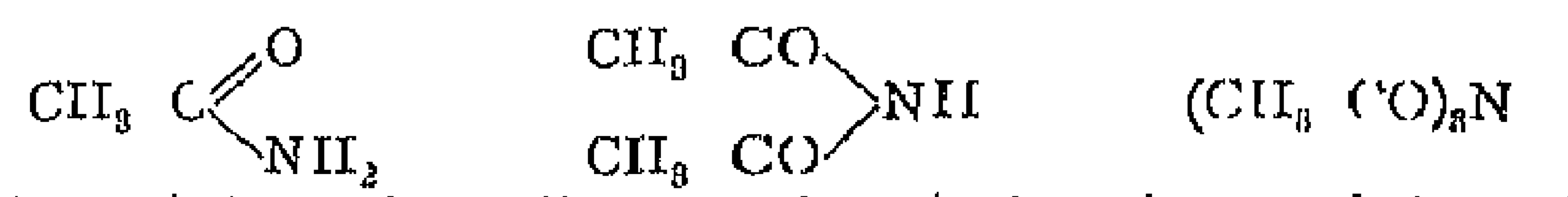
$$R \cdot Mg \cdot Br + CS_2 \longrightarrow R \cdot CS.S \cdot MgBr \longrightarrow R \cdot CS.SH$$

[1] A Pictet and Khotinsky, *Ber*, 1907, 40, 1163 [2] Pawlowski, *Ber*, 1902, 35, 110

They contain the characteristic grouping —C(:S)·SH, which appears to possess more pronounced acidic properties than the carboxyl group. The acids are exceedingly unstable and are easily oxidised in air.

6. Acid Amides

It has already been seen (p. 158) that the hydrogen of ammonia can be replaced by alkyl groups to form amines. In a similar manner the hydrogen may also be exchanged for acid radicals, when *primary*, *secondary* and *tertiary acid amides* are produced:



Acetamide (primary) Diacetamide (secondary) Triacetamide (tertiary)

If hydrogen is substituted partly by an alkyl group and partly by an acid radical, the product is termed an alkylated acid amide, *e.g.*

$$CH_3\cdot CO\cdot NH\cdot C_2H_5 \qquad CH_3\cdot CO\cdot N(CH_3)_2$$

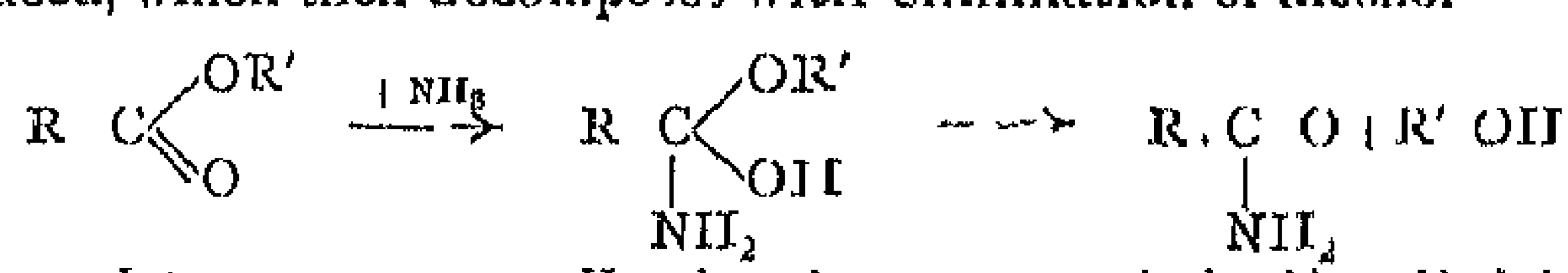
Acet-ethylamide Acet-dimethylamide

By far the most important of these compounds are the primary acid amides, commonly known as acid amides.

Derivatives of the above types are readily formed by the action of ammonia or amines on acid chlorides, anhydrides or esters:

$$CH_3\cdot CO\cdot Cl + HNH_2 = CH_3\cdot CO\cdot NH_2 + HCl$$
$$(CH_3\cdot CO)_2O + 2HNH_2 = 2CH_3\cdot CO\cdot NH_2 + H_2O$$
$$CH_3\cdot CO\cdot OC_2H_5 + HNH_2 = CH_3\cdot CO\cdot NH_2 + C_2H_5\cdot OH$$

They are generally prepared from the acid chloride and ammonia, but where this reaction does not proceed in the desired direction, an ester is used in place of the acid chloride. In the latter case the action probably takes place in two stages, an addition compound being first produced, which then decomposes with elimination of alcohol:



Ester Hypothetical intermediate product Acid amide Alcohol

In practice the reaction is best carried out by shaking the ester with concentrated aqueous ammonia in a closed vessel. Methyl esters are more completely and rapidly converted into amides than their higher homologues.[1]

The amide of an acid can often be prepared by distilling the dry ammonium salt, or more satisfactorily by heating it under pressure for about five hours at 220° to 230°.[2]

$$CH_3\cdot COONH_4 = CH_3\cdot CO\cdot NH_2 + H_2O$$

[1] Hans Meyer, *Monats.*, 1906, 27, 31. [2] H. Decker, *Ann.*, 1913, 395, 282.

Finally, acid amides can also be obtained from nitriles (cyanides), which take up the elements of water when treated with moderately strong sulphuric acid

$$\underset{\text{Methyl cyanide}}{CH_3\cdot CN} + H_2O = \underset{\text{Acetamide}}{CH_3\cdot CO\cdot NH_2}$$

Properties—With the exception of the fluid formamides, amides are colourless crystalline compounds, those of lower molecular weight being easily soluble in water. Their boiling-points lie considerably higher than those of the corresponding acids.

In connection with their chemical behaviour it should be noted that acid amides differ from amines in possessing very little basic character. While, therefore, the basic properties of ammonia are retained after the entrance of an alkyl group, they are very strongly diminished by the introduction of an acid radical. Salts such as $CH_3CO\cdot NH_2,HCl$, formed by the combination of an amide with an acid, are known, but they are very unstable and decompose into their original components on treatment with water. On the other hand, amides are also weakly acidic in character, one of the two hydrogen atoms of the amido group being replaceable by metals. Mercury salts of this type are readily formed by boiling an aqueous solution of an amide with mercuric oxide

$$2CH_3\cdot CO\cdot NH_2 + HgO = (CH_3\cdot CO\cdot NH)_2Hg + H_2O$$

A further difference between acid amides and amines is that in the former the bond between carbon and nitrogen is easily disrupted. On boiling with water, or more rapidly on heating with alkalis, the amides are hydrolysed to the acid and ammonia

$$CH_3\cdot CO\cdot NH_2 + H_2O = CH_3\cdot COOH + NH_3$$

Nitrous acid converts primary acid amides into the corresponding acids, with evolution of nitrogen. This reaction is in all respects analogous to the formation of alcohols from primary amines (p. 161)

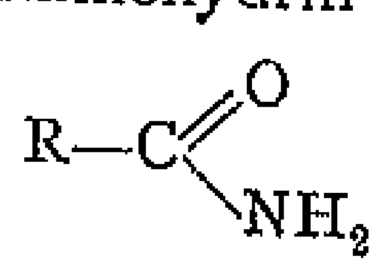
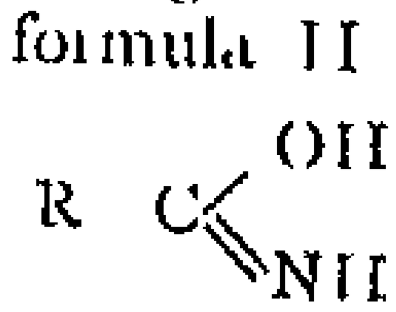
$$CH_3\cdot CO\cdot NH_2 + O{:}N\cdot OH = CH_3\cdot CO\cdot OH + N_2 + H_2O$$

Under the influence of dehydrating agents such as P_2O_5, amides are transformed into nitriles,

$$CH_3\cdot CO\cdot NH_2 - H_2O = \underset{\text{Acetonitrile}}{CH_3\cdot CN}$$

The conversion of acid amides into amines has already been described on p. 160.

With regard to the *constitution of the amides*, two formulae are theoretically possible, of which formula I is generally accepted in preference to the iminohydrin structure of formula II

I  II 

Although certain metallic derivatives of the amides,[1] such as the silver salts, appear to be related to formula II, no reactions are known which point with any degree of probability to this formula representing the constitution of the free amide. On the contrary, modern research has all tended to confirm formula I.[2]

In the case of alkylated amides, numerous and stable representatives corresponding to both types have been isolated. These derivatives are therefore structurally isomeric:

$$\underset{\text{Alkylated acid amide}}{R{-}C\begin{smallmatrix}\nearrow O \\ \searrow NHR'\end{smallmatrix}} \qquad \underset{\text{Imino ether}}{R{-}C\begin{smallmatrix}\nearrow OR' \\ \searrow NH\end{smallmatrix}}$$

The names of the acid amides, according to the Geneva nomenclature, are obtained from those of the hydrocarbons from which they are derived by the addition of the termination "amide."

Formamide, methanamide, is a liquid which is readily soluble in water and alcohol. With mercuric oxide it yields a soluble salt, $(HCO.NH)_2Hg$, and on treatment with phosphorus pentoxide it gives hydrogen cyanide.

Acetamide, ethanamide, $CH_3.CO.NH_2$, forms long needles, m.p. 82° and b.p. 222°, readily soluble in water and alcohol. It is most simply prepared by the action of ammonia on ethyl acetate.[3]

7. Amido-chlorides and Imido-chlorides

Amido-chlorides are produced by the action of phosphorus pentachloride on acid amides:—

$$CH_3.CO.NH_2 + PCl_5 = CH_3.CCl_2.NH_2 + POCl_3$$

Unless the hydrogen of the amido group is substituted by alkyl radicals, these compounds are very unstable, a molecule of hydrogen chloride first splitting off to give the more stable imido-chlorides, which finally yield nitriles.

$$\underset{\text{Amido chloride}}{CH_3.CCl_2.NH_2} \xrightarrow{-HCl} \underset{\text{Imido chloride}}{CH_3.CCl{:}NH} \xrightarrow{-HCl} \underset{\text{Nitrile}}{CH_3.C{:}N}$$

8. Imino-ethers and Amidines

As has already been mentioned, the imino-ethers are structurally isomeric with the alkylated acid amides. They are obtained in the form of hydrochlorides when carefully dried hydrochloric acid gas is led into a solution of a nitrile dissolved in the required alcohol.

$$\underset{\text{Acetonitrile}}{CH_3CN} + C_2H_5OH + HCl = \underset{\text{Acetimino ether hydrochloride}}{CH_3.C\begin{smallmatrix}\nearrow NH,HCl \\ \searrow OC_2H_5\end{smallmatrix}}$$

Most of these salts crystallise well, but are decomposed by water to form ammonium chloride and an ester. The free imino-ethers are liberated from the salts by treatment with alkali. They are basic liquids of peculiar smell, which

[1] Tafel and Enoch, *Ber.*, 1890, 23, 103. W. Wislicenus, *Ann.*, 312, 52. [2] See H. G. Rule, *J. C. S.*, 1918, 113, 3. [3] Phelps, *Amer. Journ. Science*, Silliman, [4], 1907, 24, 429.

are very sparingly soluble in water. Their properties differ considerably from those of the isomeric substituted amides. If the hydrochloride of an imino-ether is treated with ammonia, an amidine salt is formed:

$$CH_3 \cdot C\begin{matrix} \diagup NH \cdot HCl \\ \diagdown OC_2H_5 \end{matrix} + NH_3 = \underset{\text{Acetamidine hydrochloride}}{CH_3 \cdot C\begin{matrix} \diagup NH \cdot HCl \\ \diagdown NH_2 \end{matrix}} + C_2H_5 \cdot OH$$

The amidines are strong monacid bases, which are unstable in the free state, decomposing rapidly into ammonia and a nitrile or acid amide. The free compounds are only stable when the hydrogen attached to the nitrogen atoms is partially or completely replaced by alkyl groups.

9. Acid Hydrazides and Acid Azides

These substances have been investigated more particularly by Curtius and his co-workers.

The introduction of acid radicals into hydrazine results in the formation of monoacyl or primary hydrazides, $R \cdot CO \cdot NH \cdot NH_2$, and *sym.* diacyl or secondary hydrazides, $R \cdot CO \cdot NH \cdot NH \cdot CO \cdot R$.

Primary hydrazides are obtained by the action of hydrazine hydrate on esters, secondary *sym.* hydrazides being also formed as a by-product.[1] The former are of a somewhat stronger basic character than acid amides and give well-defined salts. They are easily hydrolysed, and most of them reduce ammoniacal silver nitrate in the cold. Fehling's solution is only reduced on warming.

Acid azides are produced by the action of nitrous acid on primary hydrazides:—

$$R \cdot CO \cdot NH \cdot NH_2 + HO \cdot NO = \underset{\text{Acid azide}}{R \cdot CO \cdot N\begin{matrix} \diagup N \\ \| \\ \diagdown N \end{matrix}} + 2H_2O$$

They may be considered as acyl derivatives of hydrazoic acid, N_3H. In their behaviour they resemble the corresponding acyl derivatives of hydrochloric acid, *i.e.*, the acid chlorides, although in some respects, as in their explosive properties, they show marked differences.

An interesting point in connection with the azides is that they offer a means of replacing the carboxyl group of an acid with the amino group, or in other words of passing from an acid to an amine containing one carbon atom less.[2] The procedure is indicated in the following scheme:

$$\underset{\text{Acid}}{R \cdot COOH} \longrightarrow \underset{\text{Ester}}{R \cdot COOC_2H_5} \longrightarrow \underset{\text{Hydrazide}}{R \cdot CO \cdot NHNH_2} \longrightarrow$$

$$\underset{\text{Azide}}{R \cdot CON_3} \xrightarrow[\text{with alcohol}]{\text{Treatment}} \underset{\text{Urethane}}{R \cdot NH \cdot COOC_2H_5} \xrightarrow[\text{with alkalis}]{\text{Heated}} \underset{\text{Amine}}{R \cdot NH_2}$$

If, however, the carboxyl group of the acid is united directly to a secondary carbinol group, it is possible to carry the reaction a stage further to form an aldehyde containing one carbon atom less than the original acid.[3]

$$\underset{\text{Acid}}{\begin{matrix} R \\ CH(OH) \\ COOH \end{matrix}} \longrightarrow \underset{\text{Azide}}{\begin{matrix} R \\ CH(OH) \\ CO \cdot N_3 \end{matrix}} \longrightarrow \underset{\text{Urethane}}{\begin{matrix} R \\ CH(OH) \\ NH \cdot CO_2C_2H_5 \end{matrix}} \longrightarrow \underset{\text{Amine}}{\begin{matrix} R \\ CH(OH) \\ NH_2 \end{matrix}} \longrightarrow \underset{\text{Aldehyde}}{\begin{matrix} R \\ CH:O \end{matrix}} + NH_3$$

[1] For additional methods of preparation, see Autenrieth and Spiess, *Ber.*, 1901, 34, 187.
[2] Curtius, *Ber.*, 1894, 27, 779; *J. pr. Ch.* (2), 1894, 50, 295; *Ber.*, 1896, 29, 1166.
[3] Curtius, *J. pr. Ch.*, 1904 (2), 70, 70 *et seq.*; *Ber.*, 1906, 39, 1389.

10 Aliphatic Nitriles or Alkyl Cyanides, R C N

Nitriles are formed when acid amides are heated with a dehydrating agent (P_2O_5, P_2S_5, PCl_5), or when alkyl iodides, bromides or chlorides are heated with alcoholic potassium cyanide The former method gave rise to the name of acid nitrile, *e g* acetonitrile, and the latter to that of alkyl cyanide, *e g* methyl cyanide

$$CH_3I + KCN = \underset{\substack{\text{Acetonitrile} \\ \text{or methyl cyanide}}}{CH_3 \cdot CN} + KI$$

Nitriles are also produced by the dry distillation of a mixture of potassium alkyl sulphate and potassium cyanide

$$SO_2\langle\begin{matrix} OC_2H_5 \\ OK \end{matrix} + KCN = \underset{\substack{\text{Propionitrile} \\ \text{or ethyl cyanide}}}{C_2H_5 \cdot CN} + K_2SO_4$$

The nitriles are colourless liquids or crystalline solids with a peculiar and not unpleasant smell The lower members are miscible with water, but the solubility diminishes with increasing molecular weight

When warmed with acids or alkalis they take up two molecules of water to form fatty acids of the same number of carbon atoms, a change generally known as *hydrolysis* From this it follows that the carbon of the cyanogen group is directly united to a carbon atom of the alkyl radical

$$CH_3 \cdot CN + 2H_2O = CH_3 \cdot COONH_4$$
$$CH_3 \cdot COONH_4 + KOH = CH_3 \cdot COOK + NH_3 + H_2O$$

Many reactions of the nitriles depend upon the ease with which the triple bond is converted into a double or single bond These are to be classed as *addition reactions*

Nascent hydrogen, for example, unites with nitriles to give primary amines (see p 160) For other addition reactions compare pp 168, 202 and 203

Acetonitrile, methyl cyanide, $CH_3 \cdot CN$, is a pleasant smelling liquid, b p 81°, which is usually prepared by heating acetamide with phosphorus pentoxide

Nitro-acetonitrile, $NO_2 \cdot CH_2 \cdot CN$, is obtained by removing the elements of water from methazoic acid by means of thionyl chloride[1] It is a yellow oil possessing a faint odour

Isocyanides or Carbamines, R NC

Isocyanides or carbamines are isomeric with the nitriles, from which they differ in having the nitrogen of the CN group linked directly to the alkyl radical According to the earlier work of Nef,[2] the carbon

[1] W Steinkopf and L Bohrmann, *Ber*, 1908, 41, 1044 [2] Nef, *Ann*, 1892, 270, 267

of the isocyanide group is divalent as in R N = C Later determinations of the parachors of these compounds, however, indicate that they contain a semi-polar double bond, leading to the structure R N$\stackrel{\rightarrow}{=}$C (see p 81)

They are formed together with nitriles by heating potassium cyanide with alkyl iodides or with alkali salts of alkyl sulphuric acids, and constitute the main product of reaction when an alkyl iodide is heated with cyanide of silver

Isocyanides, free from admixed nitriles, may be obtained by warming primary amines with chloroform and caustic potash (see p 123)

In their properties the carbamines differ strongly from the nitriles They are colourless liquids of extremely unpleasant odour Towards alkalis they are comparatively stable, but on treatment with acids they decompose into a primary amine and formic acid From this reaction it follows that the alkyl group is directly attached to nitrogen

$$CH_3\ NC + 2H_2O = CH_3\ NH_2 + H\ COOH$$

They yield unstable addition products with halogens and with hydrochloric acid, *e g*, $2CH_3\ NC, 3HCl$, and at high temperatures show a strong tendency to change into the isomeric nitriles

II—DERIVATIVES OF MONOCARBOXYLIC ACIDS FORMED BY SUBSTITUTION IN THE HYDROCARBON RADICAL

1 Halogen substituted Acids

Halogen substituted carboxylic acids are prepared in the same way as the corresponding derivatives of hydrocarbons

Substitution by chlorine or bromine takes place by the direct action of halogen on the acid, the degree of substitution depending on the duration of the reaction and other experimental conditions

$$CH_3\ COOH + Cl_2 = CH_2Cl\ COOH + HCl$$

The reaction proceeds slowly, but may be accelerated in various ways, among others by the addition of a "carrier" Substitution by chlorine or bromine, for example, is assisted by the addition of a small amount of iodine

If chlorine or bromine is allowed to react with a fatty acid in the presence of red phosphorus, the first step is the formation of an acid chloride or bromide The latter then undergoes substitution, which takes place more readily than in the case of the free acid

Bromination in the presence of red phosphorus (Hell-Volhard-Zelinsky method) is not only useful for the preparation of substitution products, but it often gives valuable information as to the constitution of the acid It is found that the halogen under these conditions

always replaces a hydrogen atom attached to the α-carbon atom Propionic and butyric acids, for example, yield respectively,

$$\underset{\alpha\text{-Bromo-propionic acid}}{CH_3\,CHBr\,COOH} \quad \text{and} \quad \underset{\alpha\text{-Bromo butyric acid}}{CH_3\,CH_2\,CHBr\,COOH}$$

If no hydrogen is available in the α-position, as is the case with trimethyl-acetic acid, $(CH_3)_3C\,COOH$, then no substitution takes place at all under these conditions of experiment This reaction, therefore, provides a means of establishing the presence or absence of α-hydrogen atoms in a carboxylic acid

Halogen-substituted acids can also be prepared by the direct addition of halogen or hydrogen halide to unsaturated acids, and by the action of phosphorus halides on hydroxy acids

A convenient way of obtaining α-bromo acids of the fatty series is to brominate the corresponding monoalkyl-malonic acids,[1] $R\,CH(COOH)_2$ Compounds of the general formula $R.CBr(COOH)_2$ are thus obtained in almost quantitative yield When these are heated they lose carbon dioxide and are converted into brominated acids of the type $R\,CHBr\,COOH$

Iodine-substituted acids are generally prepared from the corresponding chlorine or bromine compounds by heating with potassium iodide

$$CH_2Cl\,COOH + KI \rightarrow CH_2I\,COOH + KCl$$

Isomerism and Nomenclature—Monochloro acetic acid exists in one form only, but the mono-halogen derivatives of propionic acid and its higher homologues may occur in isomeric forms, according to the position of the halogen in the carbon chain It is usual to indicate the position of a substituent by labelling the carbon atoms $\alpha, \beta, \gamma, \delta$, etc, starting with the atom adjacent to the carboxyl group

$$\underset{\alpha\text{ Bromo propionic acid}}{CH_3\,CHBr\,COOH} \quad \underset{\beta\text{ Bromo propionic acid}}{CH_2Br\,CH_2\,COOH} \quad \underset{\gamma\text{ Bromo butyric acid}}{CH_2Br\,CH_2\,CH_2.COOH}$$

Properties—The halogenated fatty acids may be either liquids or solids On the one hand they undergo the usual reactions of carboxylic acids in forming salts, esters, chlorides and anhydrides, on the other, they resemble the alkyl halides in the reactivity of the halogen, which can readily be exchanged for hydroxy, amino and other groups Halogen-substituted acids are more strongly acidic than the parent compounds, the influence of the different halogens being in the order $Cl > Br > I$, and varying also with the number and position of the halogen atoms present Thus monochloro-acetic acid is considerably stronger than acetic acid, and the strength increases still further in di- and trichloro-acetic acids (see p 82)

The chemical properties of the substituted acids also vary con-

[1] F Fischer and W Schmitz, *Ber*, 1906, 39, 351

siderably with the position of the halogen in the molecule, as may be seen from the following

α-Halogen acids on being boiled with alkalis, or in many cases merely with water, readily exchange the halogen atom for a hydroxyl group with the formation of an α-hydroxy acid

$$CH_2Cl\cdot COOH + H_2O = \underset{\text{Hydroxy-acetic acid or glycollic acid}}{CH_2(OH)\cdot COOH} + HCl$$

β-Halogen acids, on the other hand, when heated with water lose hydrogen halide and yield unsaturated acids

$$\underset{\beta\text{-Chloro-propionic acid}}{CH_2Cl\cdot CH_2\cdot COOH} = \underset{\text{Acrylic acid}}{CH_2{:}CH\cdot COOH} + HCl$$

γ-Halogen acids under this treatment first form the corresponding γ-hydroxy acids, which then by loss of water immediately pass into lactones or cyclic anhydrides of the hydroxy acids [1]

$$\begin{array}{l}CH_3\cdot CH\cdot CH_2\cdot CH_2\cdot CO \\ \quad\;\;\; | \qquad\qquad\qquad\;\; | \\ \quad\;\; Br \qquad\qquad\quad\; HO\end{array} \longrightarrow \begin{array}{l}CH_3\cdot CH\cdot CH_2\cdot CH_2\cdot CO \\ \qquad\quad | \qquad\qquad\qquad\; | \\ \qquad\quad \text{L}\_\_\_\_\_\_\_\_\_ O\end{array}$$

Owing to their reactivity the halogen acids are of great value in organic synthesis

Monochloro-acetic acid, $CH_2Cl\cdot COOH$, is prepared by passing chlorine into hot acetic acid in the presence of phosphorus. It crystallises in needles, m p 63°

The acid has a strong corrosive action on the skin, and therefore requires careful handling. *Dichloro-acetic acid*, $CHCl_2\cdot COOH$, is best prepared by boiling chloral hydrate with aqueous sodium cyanide, and *trichloro-acetic acid*, $CCl_3\cdot COOH$, by oxidation of chloral hydrate with nitric acid

2 Esters of Nitroso- and Nitro-carboxylic Acids [2]

Preparation—When the nitrous gases obtained by heating arsenious oxide with nitric acid are led into esters of acyl-substituted fatty acids in the absence of solvents, a reaction occurs which leads to the removal of the acyl group (—CHO, —CO·CH_3, CO·C_6H_5) and the formation of nitroso derivatives of the carboxylic esters

Omitting possible intermediate products, the reaction may be represented as follows

$$\begin{array}{c}R\cdot CH\cdot COOC_2H_5 \\ | \\ Ac\end{array} \longrightarrow \begin{array}{c}R\cdot CH\cdot COOC_2H_5 \\ | \\ NO\end{array}$$

where R represents an alkyl radical and Ac an acyl group

[1] Fittig, *Ber*, 1894, 27, 2658 A detailed description of the lactones is given later, see ...
[2] J Schmidt and co workers, *Ber*, 1909, 42, 497, 1886 *Ann*, 1910, 377, 23, 30, 1913, ...

For the preparation of nitroso-carboxylic esters on a larger scale it is best to start from the corresponding acetyl derivatives, as these are well known and can generally be obtained in quantity. Methyl-acetoacetic ester, for example, is the best starting-point in the preparation of methyl-nitroso-acetic ester.

Nitroso-carboxylic esters can also be prepared in a similar manner by the replacement of inorganic acyl substituents.

Finally, it should be noted that no replacement takes place when diethyl-acetoacetic ester is submitted to the action of nitrous gases. A necessary condition for interaction is that the carbon atom to which the acyl group is attached should also be united to an alkyl radical and a hydrogen atom.

From this it may be concluded that the reaction probably takes place with the formation of an intermediate product, II, which then undergoes decomposition.

$$\underset{\text{I}}{CH_3CO\cdot\underset{H\quad R}{C}\cdot COOR} \longrightarrow \underset{\text{II}}{CH_3CO\cdot\underset{NO\quad R}{C}\cdot COOR} \longrightarrow \underset{\text{III}}{CH_3COOH + \underset{NO\quad R}{CH}\cdot COOR}$$

The *properties of nitroso-esters* are such as would be expected of true nitroso derivatives; they are blue or bluish-green oily liquids of pungent smell, which cannot be distilled without decomposition. A comparison of different alkylated nitroso-acetic esters shows that the shade of blue increases in depth as the alkyl group increases in size.

On allowing any of these compounds to stand for some time at the ordinary temperature, or more rapidly on shaking with water or alkalis, the characteristic blue colour disappears. This is partly due to intramolecular change in which the nitroso group is converted into an isonitroso group,

$$O{:}N{-}\overset{H}{\underset{CH_3}{C}}{-}COOC_2H_5 \longrightarrow HO{\cdot}N{:}\underset{CH_3}{C}{-}COOC_2H_5$$

and partly to polymerisation, as can be shown by molecular weight determinations.

Among other properties these compounds all give the Liebermann nitroso reaction. When heated with concentrated sulphuric acid and phenol and then dissolved in water, solutions are obtained which develop a blue or green colour on being made alkaline.

The constitution of the nitroso-compounds is proved on the one hand by their reduction to amino-esters, and on the other by their oxidation to the corresponding nitro-esters.

Esters of nitro-carboxylic acids are yellowish oils which require to be handled with great care, as they decompose on distillation and explode when rapidly heated.

Nitro-aliphatic Acids.—Nitro-acetic acid has been prepared by the action of potash on nitro-methane, methazoic acid being formed as an intermediate product. The potassium salt of nitro-acetic acid so obtained is then decomposed with dry hydrochloric acid.[1] *Nitro-acetic acid* is stable in the dry state and crystallises in needles, m.p. 87° to 89°. When heated in larger quantities an explosive decomposition may set in.

3. Amino Acids.[2]

Amino acids are acids in which hydrogen of the hydrocarbon radical is replaced by the monovalent amino group, $—NH_2$. They differ strongly from the corresponding acid amides, since the amino group resembles that in the amines in being firmly bound and unaffected by boiling alkalis. As in the case of the halogen acids (see p. 207), a distinction is made between α-, β-, γ-substituted acids, etc., according to the position of the substituent in the carbon chain:

$$\underset{\alpha\text{-Amino-propionic acid}}{CH_3 \cdot \overset{NH_2}{\overset{|}{C}H} \cdot COOH} \qquad \underset{\beta\text{-Amino-propionic acid}}{\overset{NH_2}{\overset{|}{C}H_2} \cdot CH_2 \cdot COOH}$$

Physiological Importance of Amino Acids.—Investigation has shown that proteins are hydrolysed by acids or alkalis, or by the ferments in the digestive tracts, to yield proteoses, peptones and finally amino acids. Of the numerous acids obtained in this manner, the constitution of the majority is now known and many have been prepared synthetically.

Monamino acids may be prepared by the following methods:

1. Aldehydes and ketones when treated with hydrogen cyanide yield cyanhydrins. These with ammonia are converted into amino-nitriles, which on hydrolysis yield α-amino acids (*Strecker*):

$$CH_3 \cdot C\begin{cases} H \\ O \end{cases} \xrightarrow{HCN} CH_3 \cdot C\begin{cases} H \\ OH \\ CN \end{cases}$$

$$\xrightarrow{NH_3} CH_3 \cdot C\begin{cases} H \\ NH_2 \\ CN \end{cases} \xrightarrow{2H_2O} CH_3 \cdot C\begin{cases} H \\ NH_2 \\ COOH \end{cases}$$

The first two phases of the above process may also be combined by treating an aldehyde or ketone directly with ammonium cyanide.[3]

An even more convenient method of effecting this synthesis is to bring equimolecular proportions of potassium cyanide and ammonium chloride into reaction with the aldehyde or ketone, in aqueous or aqueous alcoholic solution.[4]

In this case the cyanide first undergoes hydrolytic dissociation to

[1] Steinkopf and co-workers, *Ber.*, 1909, 42, 2026, 3925; 1910, 43, 3239; 1911, 44, 2891.
[2] A comprehensive survey of the amino acids will be found in a lecture by Emil Fischer "Untersuchungen über Aminosäuren, Polypeptide und Proteine," *Ber.*, 1906, 39, 530.
[3] *Ber.*, 1906, 39, 1181.
[4] *Ber.*, 1906, 39, 1722.

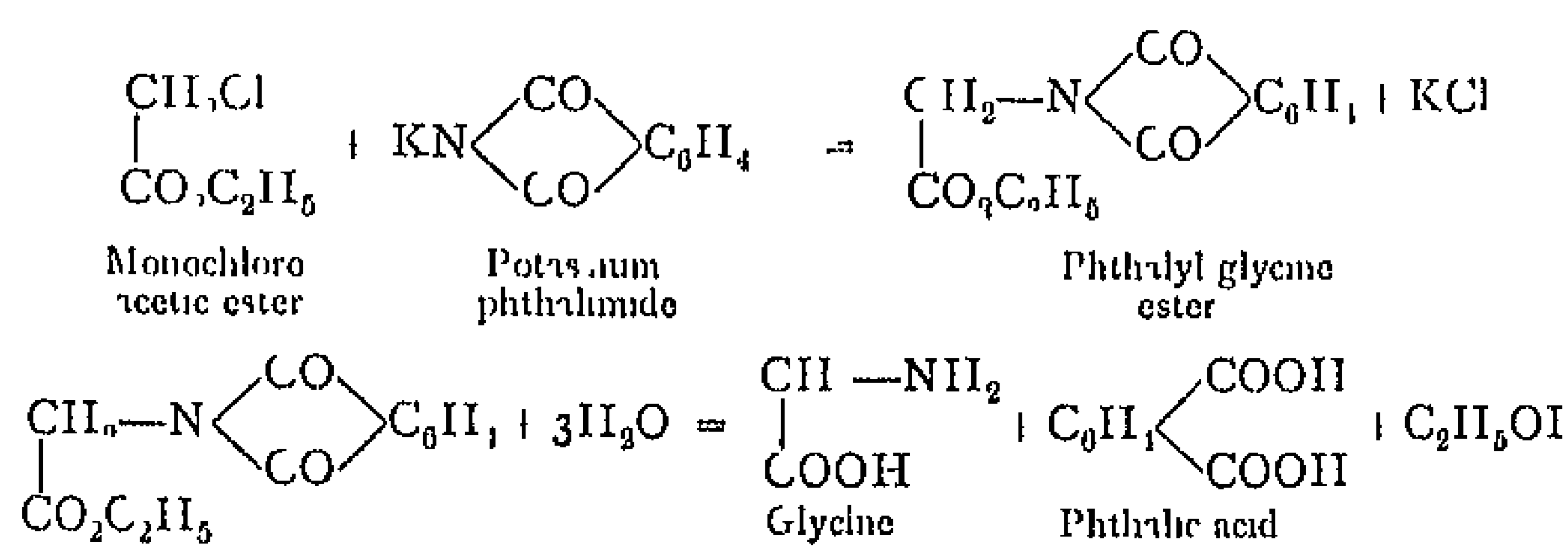
give hydrogen cyanide and potassium hydroxide, $KCN + H_2O = HCN + KOH$. The former combines with the aldehyde or ketone to yield the cyanhydrin, which is then transformed into the amino nitrile by the action of ammonia liberated from the free alkali and ammonium chloride.

2. By treating halogen substituted acids with ammonia.[1]

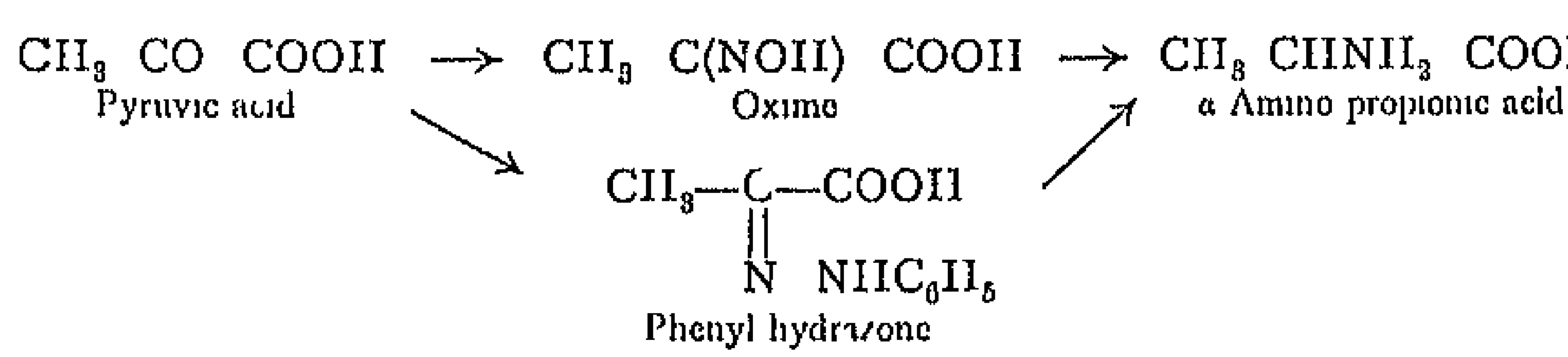
$$H_3N + Cl\cdot CH_2\cdot COOH = H_2N\cdot CH_2\cdot COOH + HCl$$

When this reaction is applied to the preparation of primary monamino acids, the latter may react further with yet unchanged halogen acid to form secondary and tertiary amino acids, such as $NH(CH_2\cdot COOH)_2$ and $N(CH_2\cdot COOH)_3$.

In order to avoid these by-reactions in the preparation of primary α-amino acids, potassium phthalimide may be used in place of ammonia (*Gabriel*). The pure amino acid is then obtained from the product so formed by heating it to 200° with hydrochloric acid (see also p. 445).



3. From ketonic or aldehydic acids (oxo-acids) by conversion into the oximes or hydrazones, followed by reduction, preferably by means of aluminium amalgam.[2]



The synthesis of α-amino acids by the reduction of the corresponding oximes may be employed with advantage in all cases where the α-ketonic acid is easily prepared.[3] The catalytic reduction of a ketonic acid dissolved in aqueous or alcoholic ammonia also yields the corresponding amino-acid.[4]

For further methods of obtaining monamino acids see E. Erlenmeyer, *Ann.*, 1905, **337**, 205; J. v. Braun, *Ber.*, 1907, **40**, 1834.

[1] E. Fischer and Schmitz, *Ber.*, 1906, **39**, 351. [2] E. Fischer and R. Groh, *Ann.*, 1911, **383**, 363. [3] Compare Knoop and Hoessli, *Ber.*, 1906, **39**, 1477. [4] Knoop and Oesterlin, *Z. physiol. Ch.*, 1925, **148**, 294.

Diamino acids are in general more difficult to prepare than monamino acids

1 A modified form of the phthalimide method described above is available for the preparation of these compounds Thus, for example, $\alpha\delta$ diamino-valeric acid may be synthesised from phthalimido-propyl-malonic ester, $C_6H_4\langle{}^{CO}_{CO}\rangle N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(COOC_2H_5)_2$ The latter readily forms a bromo derivative, which after hydrolysis and splitting off carbon dioxide yields phthalimido-bromo-valeric acid, $C_6H_4 \cdot C_2O_2 \cdot N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CHBr \cdot COOH$ From this, by the action of ammonia and removal of the phthalyl radical, is obtained $\alpha\delta$-diamino-valeric acid, $NH_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, which is the racemic form of the naturally occurring ornithine[1] (see p 219)

2 Another and somewhat similar process has been developed by Sorensen[2]

3 Diamino acids are also formed by the action of ammonia on acids containing two ethylene bonds Thus on heating sorbic acid with ammonia a diamino-caproic acid is produced[3]

4 Amino acids are largely prepared by hydrolysing proteins with mineral acid and separating the resulting mixture by Fischer's ester method (see p 214) A further method of isolation has been described by *Dakin*[4] It consists in removing the monamino acids and proline by *continuous extraction with butyl alcohol*, the diamino acids and the monamino dicarboxylic acids remain in the aqueous layer, from which they can be separated This process has the advantage that optically active acids are not racemised

Properties and Constitution of Amino Acids—The majority of the amino acids are crystalline compounds, often of sweet taste, which are soluble in water but insoluble in alcohol and ether

They are both basic and acidic in character, and therefore form salts with acids as well as with bases Simple monamino acids are neutral in reaction, and it has been assumed that the carboxyl and amino groups neutralise each other within the molecule to form an inner salt Opinion as to their constitution is at present divided According to the older view their properties are represented by the formula I (amino-acetic acid being used as an example), in which the amino and carboxyl groups are supposed to be free According to modern ideas a compound of this type is considered unstable, as the amino group would probably have a strong tendency to unite with the carboxyl group to form a cyclic ammonium salt When the amino acid is converted into a salt by combination with another acid or base, a separation of the NH_2 and COOH groups takes place These views

[1] E Fischer, *Ber*, 1901, 34, 454. [2] *C*, 1908, II, 681 [3] E Fischer und Schlotterbeck, *Ber*., 1904, 37, 2357 [4] *Biochem J*, 1918, 12, 290

are expressed in II, which is known as the *betaine formula* for amino acids

$$\text{I}\quad \begin{array}{l} COOH \\ | \\ CH_2{-}NH_2 \end{array} \qquad\qquad \text{II}\quad \begin{array}{l} CO - O \\ |\qquad | \\ CH_2{-}NH_3 \end{array}$$

Among other facts supporting this structure may be mentioned the existence and mode of formation of trimethyl-glycine or betaine (see p 218) It has not yet been found possible to isolate an amino-acid in two desmotropic forms, and hence the above two formulæ must for the present be regarded as equally well justified

As amino acids are neutral in reaction they cannot be directly titrated with alkalis Use may be made of *Sorensen's formal titration method*, in which the basic amino group is modified by interaction with formaldehyde, giving a relatively strong acid which may be titrated in the usual way

$$\begin{array}{l} CH_3 \\ | \\ CH\ NH_2 \\ | \\ COOH \end{array} + H\ CHO = \begin{array}{l} CH_3 \\ | \\ CH\ N\ CH_2 \\ | \\ COOH \end{array} + H_2O$$

The *hydrogen of the amino group* in these acids may be replaced by an alkyl radical or by an acyl group In the latter case the compound formed is both an acid amide and an amino acid, *e g*,

$$R\ CO\ Cl + H_2N\ CH_2\ COOH = R\ CO\ NH\ CH_2\ COOH + HCl$$

Prominent among compounds of this type are the benzoyl derivatives, which according to E Fischer may be used in resolving racemic amino acids into their optically active components Unlike the amino acids, the benzoyl compounds are strongly acidic and can be combined with an optically active base The mixture of salts thus formed from a racemic acid can then be separated by fractional crystallisation (*cf* p 41), and the active benzoyl compounds converted by hydrolysis into the active amino acids

The corresponding *compounds of amino acids with β-naphthalene sulphonic acid* are distinguished by their small solubility in water, and are therefore useful for the isolation and identification of amino acids [1]

Amino acids unite with phenyl isocyanate to form *phenylureido-acids*,[2] *e g*

$$\underset{\text{Phenyl isocyanate}}{C_6H_5NCO} + \underset{\text{Amino acetic acid}}{H_2N\ CH_2\ COOH} = \underset{\text{Phenylureido acetic acid}}{C_6H_5\ NH\ CO\ NH\ CH_2\ COOH}$$

Owing to their low solubility these compounds and the corresponding substances formed with α-naphthyl-isocyanate, $C_{10}H_7NCO$, are used in the separation of amino acids [3]

[1] E Fischer and Bergell, *Ber*, 1902, 35, 3779 [2] Paal, *Ber*, 1894, 27, 974 [3] Neuberg and Manasse, *Ber*, 1905, 38, 2359

In the case of diamino acids the best means of separation is *precipitation with phosphotungstic acid*[1]

Most amino acids yield a sparingly soluble *copper salt*

Esters of amino acids may be prepared by leading hydrochloric acid gas into a solution of the acid in absolute alcohol The hydrochlorides so formed (*e g*, $HCl, NH_2 \cdot CH_2 \cdot COOC_2H_5$) are decomposed with concentrated alkali at a low temperature and the free ester, ($NH_2 \cdot CH_2 \cdot COOC_2H_5$), extracted with ether[2]

Owing to their property of distilling without decomposition, the esters are of great service in separating the mixtures of amino acids produced by the hydrolysis of proteins (*Fischer*) Amino-esters are exclusively basic in character, and in their reactions strongly resemble primary amines They yield acid amides on treatment with liquid ammonia, and as is described in more detail below, can be converted into *diketo piperazines*

The *chlorides of amino acids*, containing the group COCl in place of carboxyl, are, according to Fischer,[3] best prepared by shaking the acid at 0° to 20° with about 10 to 15 times the theoretical amount of acetyl chloride and the calculated amount of phosphorus pentachloride Under these conditions the hydrochloride of the acid chloride is obtained, of the general formula $\begin{array}{c} R \cdot CH \cdot COCl \\ | \\ NH_3Cl \end{array}$ Compounds of this type possess the reactivity of ordinary acid chlorides and, as will be seen later, may be used in the synthesis of polypeptides

Action of Yeast and Moulds on Amino Acids—It has already been stated on p 143 that fermenting yeast in the presence of sugar converts amino acids into alcohols, and that this process can be used for preparing alcohols from amino acids Certain moulds, such as *oidium lactis*, effect the removal of the ammonia required as nutriment in a somewhat different manner,[4] the elements of water being added during the process, according to the equation

$$R \cdot CH(NH_2) \cdot CO_2H + H_2O = R \cdot CH(OH) \cdot CO_2H + NH_3$$

During the growth of the fungus the chain of carbon atoms remains practically unaltered, and an almost quantitative yield of α-hydroxy acid can be isolated from the solution In this case only very small amounts of alcohol are produced Since any desired quantity of an amino acid may be transformed in a comparatively short time by means of *oidium lactis*, we have here a convenient way of preparing optically active hydroxy-acids from active or racemic amino

[1] For further details see E Fischer and Abderhalden, *Z physiol Ch*, 1903, 39, 88; E Fischer, *Ber*, 1906, 39, 547, Levene and Beatty, *Z physiol Ch*, 1906, 47, 149 [2] E Fischer, *Ber*, 1901, 34, 433 In place of potassium hydrate, lead hydroxide may conveniently be used (*Z physiol Ch*, 1911, 73, 159) [3] E Fischer, *Ber*, 1906, 39, 545 [4] F Ehrlich, *Ber*, 1911, 44, 139, 888

acids, a method which has many advantages over purely chemical processes.

The *bacterial fermentation of amino acids*, which takes place in the intestinal canal, leads to a variety of products including phenols, mono- and di-amines and fatty acids. The connection between these compounds and particular amino acids can usually be deduced from the constitution of the latter, and has in many cases been proved experimentally.

The *degradation of the amino acids by animal cells* occurs by way of decarboxylation or by oxydative de-amination, amides or ketonic acids being thus formed as intermediate products.

By application of the *Grignard reaction to amino-esters* it is possible to obtain amino-alcohols.[1]

As in the case of the halogen acids (p. 208), the chemical behaviour of amino acids varies with the position of the amino group in the carbon chain.

a-Amino acids readily lose two molecules of water from two molecules of acid, or two molecules of alcohol may be eliminated from two molecules of amino-ester, to form cyclic anhydrides called 2 : 5-*diketo-piperazines*. These possess the properties of acid amides.[2]

$$\begin{array}{l} CH_2\cdot NHH \\ | \\ CO\cdot OC_2H_5 \end{array} + \begin{array}{r} C_2H_5O\cdot CO \\ | \\ HHN\cdot CH_2 \end{array} = \begin{array}{l} CH_2\cdot NH\cdot CO \\ |\qquad\qquad | \\ CO\cdot NH\cdot CH_2 \end{array} + 2C_2H_5OH$$

Glycine anhydride, 2 : 5-diketo-piperazine

β-Amino acids readily part with ammonia to yield *unsaturated acids*:

$$H_2N\cdot CH_2\cdot CH_2\cdot COOH = CH_2{:}CH\cdot COOH + NH_3$$

β-Amino-propionic acid — Acrylic acid

γ- and δ-amino acids, and those with longer chains, are easily converted by loss of water into inner anhydrides termed *lactams*. These are cyclic acid amides which correspond to the lactones or cyclic anhydrides of hydroxy acids.

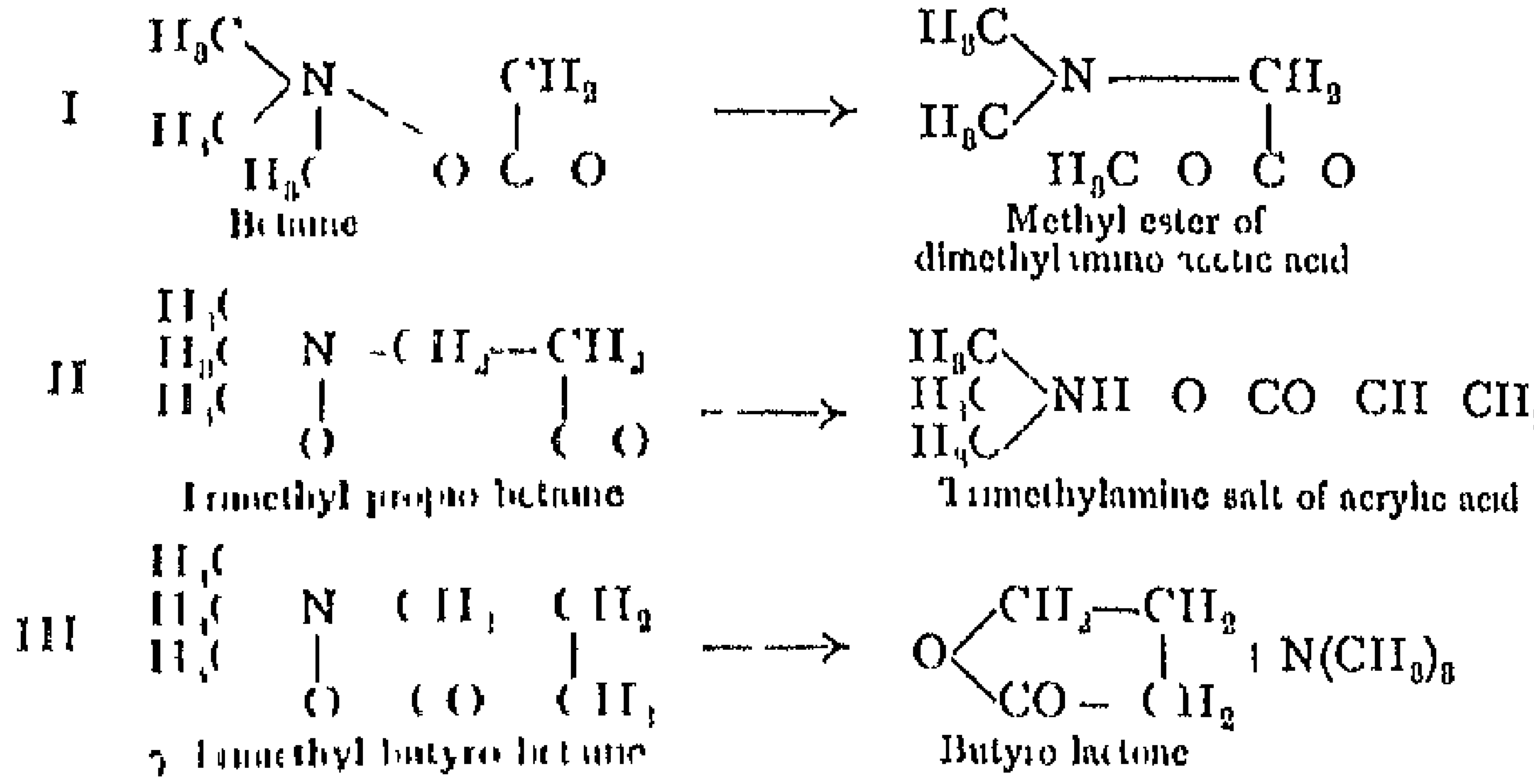
$$\begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO \\ | \qquad\qquad\qquad | \\ NHH \qquad\qquad\quad OH \end{array} = \begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO \\ | \qquad\qquad\qquad | \\ NH \text{———————} \end{array} + H_2O$$

γ-Amino-butyric acid — γ-Butyro-lactam or pyrrolidone

A comparison of the behaviour of the completely alkylated compounds, known as betaines, under the influence of heat, shows even more clearly how the position of the amino group affects the properties. *a*-Betaines on fusion are converted smoothly into esters of tertiary amino acids (I), the simplest *β*-betaine, propio-betaine, isomerises to form the trimethylamine salt of acrylic acid (II),

[1] Paal and Weidenkaff, *Ber.*, 1906, 39, 810. [2] E. Fischer, *Ber.*, 1906, 39, 556.

and butyro-betaine, a γ-betaine, decomposes into butyro-lactone and trimethylamine (III)



Action of Sodium Hypochlorite on α-Amino Acids[1]—Hypochlorites react with α-amino acids in the same way as with simple amines. According to the amount of hypochlorite employed, and the number of hydrogen atoms directly attached to nitrogen, there are formed mono- or dichloro substitution products. Further action results in oxidation and the formation of an aldehyde containing one atom of carbon less than the original acid, *e.g.*,

$$CH_3 \cdot CH(NH_2) \cdot COOH \longrightarrow CH_3 \cdot CHO$$

Glycine, glycocoll, *amino acetic acid, amino ethanic acid* $\begin{array}{l} COOH \\ | \\ CH_2 \cdot NH_2 \end{array}$ or $\begin{array}{ll} CO & O \\ | & | \\ CH_2 & NH_3 \end{array}$, melts at [illegible] to 236°, and is formed by the general methods already described. It may be prepared by boiling glue with dilute sulphuric acid or baryta (hence its name), also from its benzoyl derivative *hippuric acid*, which occurs in the urine of horses, by hydrolysis with hydrochloric acid[2]

$$C_6H_5 \cdot CO \cdot NH \cdot CH_2 \cdot COOH + H_2O + HCl \longrightarrow HCl, NH_2 \cdot CH_2 \cdot COOH + C_6H_5 \cdot COOH$$

[illegible] glycine [illegible] Glycine hydrochloride Benzoic acid

When benzoic acid is introduced into the human organism it also becomes [illegible] and eliminated in the urine as hippuric acid. Similarly [illegible] removed from the animal organism in the form of *phenaceturic acid*, [illegible] $CH_2 \cdot COOH$. It is believed that such changes are part of [illegible] by which foreign substances are rendered harmless and removed [illegible]. In birds, ornithine (p. 219) plays the part of glycine in the above [illegible] being eliminated as *ornithuric acid* (dibenzoyl ornithine)

[1] [illegible] 42, 394, 2360. [2] For further methods see E. Erlenmeyer, jun., [illegible] 85, 2418.

Glycine forms large rhombic crystals, dissolves easily in water and is insoluble in alcohol and ether. It possesses a sweet taste, and gives a characteristic dark blue crystalline *copper salt*, of the composition $(NH_2\cdot CH_2\cdot COO)_2Cu + H_2O$. The latter is readily soluble in water and is formed when a solution of glycine is boiled with copper carbonate. The *ethyl ester* boils at 51.5° to 52.5° under 10 mm, and when reduced in neutral solution by means of sodium amalgam yields amino acetaldehyde.[1]

Aliphatic Diazo compounds.—Nitrous acid interacts with glycine ester to give diazo compounds which are acid derivatives of diazo methane (p. 165). The hydrochloride of glycine ester when treated with sodium nitrite yields **diazoacetic ester**, b.p. 140° under 720 mm. The latter is a yellow oil which is insoluble in water.

$$C_2H_5OOC\cdot CH_2\cdot NH_2\cdot HCl + NaNO_2 = \underset{\text{Diazoacetic ester}}{C_2H_5OOC\cdot CH\left\langle\begin{array}{c}N\\ \|\\ N\end{array}\right.} + NaCl + 2H_2O$$

Diazo compounds of analogous constitution are also formed by the action of nitrous acid on other amino acids.[2]

Investigation has shown that only esters of α-amino acids can be converted into diazo esters. No diazo compounds have been isolated from free amino acids or from esters of β- or γ-amino acids. In addition, it is necessary that at least one hydrogen atom should be united to the carbon atom linked to the amino group, in order to permit the formation of the azo methane ring with nitrous acid by loss of two molecules of water. The most stable diazo compounds are obtained from substances such as glycine ester, which contain the group $—CH_2\cdot NH_2$, and thus form derivatives in which a hydrogen atom still remains attached to the carbon of the azo methane ring.

Aliphatic diazo esters are very reactive, nitrogen being readily eliminated and its place taken by two monovalent atoms or groups.

A point of special interest is the use of diazoacetic ester in the preparation of *diamide* or *hydrazine*, $NH_2\cdot NH_2$, and the conversion of the latter into *hydrazoic acid*, N_3H (*Curtius*), also the synthesis of pyrazole derivatives (see index) from the same starting material.[3] On reduction, diazoacetic ester is converted into hydrazino acetic ester,[4] $NH_2\cdot NH\cdot CH_2\cdot COOC_2H_5$.

Recently the poly glycine esters (p. 221) have also been converted into diazo-esters (Curtius), *e.g.*,

$$\underset{\text{Glycyl glycine ester}}{H_2NCH_2CO\cdot NHCH_2CO_2C_2H_5} \longrightarrow \underset{\text{Diazo acetylamino acetic ester}}{N_2\colon CHCO\cdot NHCH_2CO_2C_2H_5}$$

These compounds undergo the same reactions as diazoacetic ester, and are therefore valuable in synthesis.[5]

[1] E. Fischer, *Ber.*, 1908, **41**, 1019. C. Neuberg, *ibid.*, 956.
[2] See Curtius, "Ueber Hydrazin, Stickstoffwasserstoff und die Diazoverbindungen der Fettreihe," *Ber.*, 1896, **29**, 759. Curtius and Müller, "Neue Untersuchungen über Diazofettsäureester," *Ber.*, 1904, **37**, 1261. For isodiazoacetic ester, see Hantzsch and Lehmann, *Ber.*, 1901, **34**, 2506, and for the polymerisation products of diazoacetic ester, Hantzsch and Silberrad, *Ber.*, 1900, **33**, 58.
[3] E. Buchner, *Ann.*, 1887, **237**, 214.
[4] Darapsky and Prabhakar, *Ber.*, 1912, **45**, 1654, 2617.
[5] Curtius and co-workers, *Ber.*, 1904, **37**, 1261; 1906, **39**, 1373.

Methyl-glycine, *sarcosine*, $\begin{array}{l}COOH\\ |\\ CH_2\cdot NH\cdot CH_3\end{array}$ or $\begin{array}{l}CO - O\\ |\quad\;\; |\\ CH_2-NH_2\cdot CH_3\end{array}$,

is formed from *creatine* (see p 335), $\begin{array}{l}\qquad\qquad\; COOH \qquad NH_2\\ \qquad\qquad\; | \qquad\qquad\;\; |\\ CH_2\cdot N(CH_3)\cdot C=NH\end{array}$, which is present in meat juice, or from the alkaloid *caffeine* by warming with baryta water Synthetically it may be prepared by the action of methylamine on chloroacetic acid It melts at 210°, dissolves readily in water and sparingly in alcohol With cyanamide it combines to form creatine

Trimethyl-glycine, betaine, $\begin{array}{l}CO - O\\ |\qquad\; |\\ CH_2-N(CH_3)_3\end{array}$, is present in cotton-seed, in the embryo of wheat and barley, and in the sugar beet In the manufacture of sugar from the latter source the betaine collects in the molasses Betaine is produced by the oxidation of choline and may be obtained synthetically from trimethylamine and chloroacetic acid[1] These methods of preparation confirm the above structural formula All compounds of similar constitution, *i e* all internal salts of ammonium bases, are known under the general names of betaines (see p 213)

Betaine crystallises in large crystals containing one molecule of water, which may be removed over sulphuric acid or at 100° The anhydrous compound melts at 293°, being transformed into the *methyl ester of dimethyl amino acetic acid*,[2] and on further heating decomposes with formation of trimethylamine On the technical scale trimethylamine is prepared by heating the molasses from beet sugar Betaine can also be converted into glycollic acid by heating with caustic soda, or by the action of certain moulds[3]

Alanine, *α-amino-propionic-acid*, $CH_3\cdot CH(NH_2)\cdot COOH$, which only occurs in the *d*-form in nature, is obtained from α-chloro- or α-bromo-propionic acid and ammonia On treatment with nitrous acid it is converted into lactic acid (p 227) Transitions between alanine and lactic acid have also been detected in the animal organism These changes are of interest because they establish for the first time an undoubted connection between a lower degradation product of proteins and a simple product of carbohydrate metabolism Natural dextro-rotatory alanine is best prepared by the hydrolysis of silk Owing to its relationship to *l*-glyceric aldehyde (adopted as a standard in determining the configuration of sugars and optically active acids) the natural alanine is now more correctly described as *l*(+)-alanine[4] (compare sugars, p 288)

***l*-Leucine**, *α-amino-isobutyl-acetic acid*, *α-amino-isocaproic acid*, $(CH_3)_2CH\cdot CH_2\cdot CH(NH_2)COOH$, occurs in the pancreas and spleen, and is formed in considerable quantity when proteins are decomposed

[1] Willstätter, *Ber*, 1902, 35, 603 [2] Willstätter, *Ber*, 1902, 35, 603 [3] Ehrlich and Lange, *Ber*, 1913, 46, 2746 [4] Freudenberg and Rhino, *Ber*, 1924, 57, 1547

with acids or alkalis, or by putrefaction. It can be prepared from horn or casein by heating with dilute sulphuric acid. In this manner it is obtained as a white crystalline product, m.p. 270°, which is optically active. Leucine and its pale blue copper salt are both sparingly soluble in water. The inactive form may be prepared by interaction of isovaleraldehyde, ammonia, and hydrogen cyanide, by hydrolysis of the condensation product of isobutyraldehyde and hippuric acid,[1] or by reduction of α-oximino-isobutyl acetic ester with sodium amalgam.[2]

$$\underset{\text{Isovaleraldehyde}}{(CH_3)_2CHCH_2CH{:}O} \xrightarrow{NH_4CN}$$

$$\underset{i\text{-Leucine}}{(CH_3)_2CHCH_2CH\begin{matrix}\diagup NH_2\\ \diagdown COOH\end{matrix}} \xleftarrow{\text{Reduction}} \underset{\alpha\text{-Oximino-isobutyl acetic ester}}{(CH_3)_2CHCH_2C\begin{matrix}\diagup\!\!\diagup NOH\\ \diagdown COOC_2H_5\end{matrix}}$$

d-**Isoleucine**, *α-amino-β-methyl-β-ethyl-propionic acid*, $(CH_3)(C_2H_5)CH \cdot CH(NH_2)COOH$, is found in nature associated with leucine, which it strongly resembles. It may be obtained from the strontium liquors used in refining sugar and by various synthetic methods. A simple method of preparation is from malonic ester and secondary butyl iodide in the following stages:[3]

$$C_2H_5 \cdot CHI \cdot CH_3 + CHNa(CO_2C_2H_5)_2 \rightarrow C_2H_5 \cdot CH(CH_3) \cdot CH(CO_2C_2H_5)_2 \rightarrow$$
$$C_2H_5 \cdot CH(CH_3) \cdot CH(CO_2H)_2 \rightarrow C_2H_5 \cdot CH(CH_3) \cdot CBr(CO_2H)_2 \rightarrow$$
$$C_2H_5 \cdot CH(CH_3) \cdot CHBr \cdot CO_2H \rightarrow C_2H_5 \cdot CH(CH_3) \cdot CH(NH_2) \cdot CO_2H$$

δ-Amino-n-valeric acid, $NH_2 \cdot CH_2 \cdot (CH_2)_3COOH$, m.p. 158°, has been isolated from the products of putrefaction of fibrin and flesh.

In addition to these monamino acids, the majority of albuminous substances also contain varying amounts of **diamino acids**. According to Kossel, the latter predominate in the protamines. The following three compounds have been carefully investigated: Ornithine, lysine and arginine.

The diamino acids are distinguished from the monamino acids by their alkaline reaction, resulting from the amino group which is not neutralised by intramolecular union. On putrefaction they undergo decarboxylation to yield diamines such as putrescine and cadaverine (p. 241).

Ornithine, *αδ-diamino-valeric acid*, $H_2N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH(NH_2)COOH$, was first obtained by the hydrolysis of its dibenzoyl compound *ornithuric acid*, which occurs in the excrement of hens fed with benzoic acid (see p. 216). The product so obtained is optically active. The

[1] F. Erlenmeyer, jun., and Kunlin, *Ann.*, 1901, 316, 145. [2] Bouveault and Locquin, *C. r.*, 1904, II, 1710. For the resolution of racemic leucine see Warburg, *Ber.*, 1905, 38, 187; E. Fischer and Warburg, *Ber.*, 1905, 38, 3997. [3] F. Ehrlich, *Ber.*, 1908, 41, 1453.

racemic form of ornithine has been synthesised by E Fischer[1] according to method 2 on p 212, and resolved into its optically active components by Sörensen by way of the dibenzoyl compound

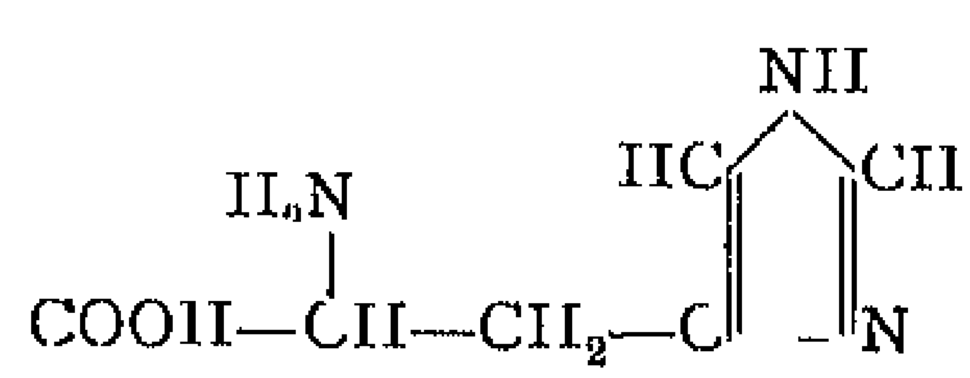
Arginine, *α-amino δ-guanido-valeric acid*,

$$\begin{matrix} HN \\ H_2N \end{matrix}\!\!>\!C\ \ NH\ \ CH_2\ \ CH_2\ \ CH_2\ \ CH(NH_2)COOH$$

is found among the hydrolytic products of many animal proteins, and is also contained in the cotyledons of etiolated lupins It is closely related to ornithine, since on hydrolysis with barium hydroxide or by the action of the enzyme *arginase* it yields a mixture of ornithine and urea Arginine has been synthesised by the combination of cyanamide CN NH_2 and ornithine[2] It is usually prepared from the protein edestin by hydrolysis with fuming hydrochloric acid

Lysine, *αε-diamino-caproic acid*, NH_2 $CH_2(CH_2)_3$ $CH(NH_2)COOH$ was discovered by Drechsel as a hydrolytic product of casein, and has been found by other workers among the products of acid hydrolysis of all proteins subsequently examined The compound so obtained is dextro-rotatory Pancreatic decomposition converts it into pentamethylene-diamine or cadaverine, NH_2 $CH_2(CH_2)_3CH_2$ NH_2 Fischer and Weigert prepared the racemic form of lysine by reducing α-oximino-γ-cyano valeric acid[3]

Histidine is also a common decomposition product of proteins, and is an *α-amino-β-iminazyl propionic acid* of the formula



It has been synthesised by Pyman[4]

Hydroxy-, thio-, dibasic and cyclic amino-acids are described under their appropriate headings

POLYPEPTIDES

It has already been stated that amino acids predominate among the hydrolytic products of proteins, and for a long time attempts were made on the part of various investigators to bring these again into combination by anhydride formation, with the object of building up larger molecules The results obtained, however, were not satisfactory

Emil Fischer was the first to develop methods by which the molecules of various amino acids could be successively linked on to

[1] E Fischer, *Ber*, 1901, 34, 454 Fischer and Zemplén, *Ber*, 1909, 42, 1022 [2] E Schulze and E Winterstein, *Ber*, 1899, 32, 3191 For the synthesis of arginine from ornithine and ..., cf Sörensen and M Hoyrup, *Ber*, 1910, 43, 643 [3] For a synthesis of inactive lysine from piperidine, see J v Braun, *Ber*, 1909, 42, 839 [4] Pyman, *J C S*, 1916, 109, 186

one another in a species of amide formation, each intermediate substance being isolated and identified. The resulting products, whose simplest representative is glycyl-glycine $NH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOH$ obtained from glycine, were described under the collective name of polypeptides. According to the number of amino-acid residues contained in the molecule, they are distinguished as di-, tri-, tetra-peptides, and so on.

In connection with these compounds Fischer writes: "The higher members of this synthetic series are, with respect to their external properties, certain colour reactions, and behaviour towards acids, alkalis, and ferments, so similar to the natural peptones that they may be considered as their nearest relatives, and I regard their synthesis as the first step in the production of natural peptones and albumoses."

Synthesis of Polypeptides[1]

1. Dipeptides can be prepared by the hydrolysis of 2 : 5-diketo-piperazines. As stated on p. 215, the latter are obtained from α-amino acids by loss of 2 mols. water, or from the corresponding esters by loss of 2 mols. alcohol.

Glycine anhydride, the simplest 2 : 5-diketo-piperazine, formed the starting-point of Fischer's investigations. When this compound is boiled for a short time with concentrated hydrochloric acid or shaken with cold dilute alkali, the ring is opened up and a hydrochloride or salt of glycyl-glycine is obtained:

$$\underset{\text{2 : 5-Diketo-piperazine, glycine anhydride}^{2}}{\begin{array}{ccc} HN & \cdot CH_2 \cdot & CO \\ | & & | \\ OC & \cdot CH_2 \cdot & NH \end{array}} + H_2O = \underset{\text{Glycyl-glycine}}{H_2N \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOH}$$

By using alcoholic hydrochloric acid in place of aqueous acid, the 2 : 5-diketo-piperazine may be converted directly into glycyl-glycine ester, $NH_2 \cdot CH_2 \cdot CO \cdot NH \cdot CH_2 \cdot COOC_2H_5$.

2. More complex compounds can in many cases be prepared by elimination of one molecule of alcohol from two molecules of amino-esters or esters of higher polypeptides.[3] For example, the methyl ester of diglycyl-glycine at 100° quickly reacts according to the equation:

$$2NH_2CH_2CO \cdot NHCH_2CO \cdot NHCH_2CO_2CH_3 \\ = CH_3OH + NH_2CH_2CO \cdot (NHCH_2CO)_4 \cdot NHCH_2CO_2CH_3$$

to form the methyl ester of a hexapeptide, from which the hexapeptide itself may be obtained by hydrolysis.

[1] For full details reference should be made to the lecture by Emil Fischer "Untersuchungen über Aminosäuren, Polypeptide und Proteïne," *Ber.*, 1906, **39**, 530. See also Curtius, *J. pr. Ch.*, 1904 (2), **70**, 57. [2] With reference to an anhydride of glycine which is not 2 : 5-diketo-piperazine, see H. Leuchs, *Ber.*, 1906, **39**, 857. [3] Curtius, *Ber.*, 1904, **37**, 1300.

3 Dipeptides are obtained by bringing amino acids or their esters into reaction with halogen-substituted acid chlorides, and treating the product with ammonia For example, chloro-acetyl chloride $ClCH_2\ COCl$ reacts with glycine to give *chloro-acetyl-glycine*, which with ammonia yields *glycyl-glycine*

$$\underset{\text{Chloro acetyl glycine}}{Cl\ CH_2\ CO\ NH\ CH_2\ COOH} + 2NH_3 = \underset{\text{Glycyl-glycine}}{NH_2\ CH_2\ CO\ NH\ CH_2\ COOH} + NH_4Cl$$

Glycyl glycine may be once again combined with chloro-acetyl chloride and the product treated with ammonia, when diglycyl-glycine is obtained —

$$\underset{\text{Diglycyl-glycine}}{H_2NCH_2CO\ NHCH_2CO\ NHCH_2COOH}$$

This synthesis has been continued to the stage of a pentapeptide and could probably be carried on still further Most of the polypeptides at present known have been obtained by this method, since it is possible to employ as components a variety of substituted acid chlorides on the one hand, and on the other ordinary amino acids, hydroxy-amino acids (see index), and still more complicated substances, such as cystine

4 The amino acid chain may also be extended on the side of the carboxyl group Of the processes available for this purpose, the following is of most importance in the synthesis of polypeptides When amino acids are shaken with acetyl chloride and phosphorus pentachloride, they are converted into hydrochlorides of the corresponding amino-acid chlorides (p 214), which readily couple up with esters of amino acids or polypeptides Thus the chloride of α-bromo isocaproyl-glycine reacts with glycine ester according to the following equation —

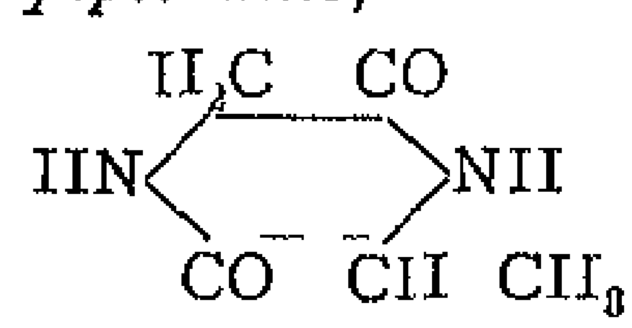
$$C_4H_9\ CHBr\ CO\ NH\ CH_2\ CO\ Cl + 2NH_2\ CH_2\ CO_2C_2H_5$$
$$= HClNH_2\ CH_2\ CO_2C_2H_5$$
$$+ C_4H_9\ CHBr\ CO.NH\ CH_2\ CO\ NH\ CH_2CO_2C_2H_5$$

By hydrolysis of the ester so obtained and subsequent treatment with ammonia it is converted into *leucyl-glycyl-glycine*

This method is of special importance in its application to optically active amino acids, whereby optically active polypeptides are produced. Such compounds are of unusual interest because the naturally occurring proteins as well as their products of hydrolysis—albumoses, peptones, etc—are also active The methods just described were first applied to monamino acids, and with the exception of the fourth, have also been extended to diamino and hydroxy-amino acids Up to the present over a hundred polypeptides of different composition have been prepared by these means.

In his researches on the polypeptides Fischer finally succeeded in 1907 in building up an *octadekapeptide* containing fifteen glycine and three leucine residues, thus effecting the synthesis of the most complex organic substance whose constitution was then known. In its general properties this polypeptide of molecular weight 1213 shows the greatest similarity to many naturally occurring proteins. Nine years later E. Abderhalden carried the synthesis a step further, and by the same method prepared a peptide with 19 amino-acid residues, containing one leucine residue more than Fischer's octadekapeptide. Some idea of the complexity of these substances may be gained from the fact that according to Fischer's calculations 816 isomeric octadekapeptides of the same composition are possible. For the polypeptide obtained by Abderhalden the number of isomerides has increased to 3876.

A discovery of some importance was the isolation in considerable quantity of a *methyl diketo-piperazine*,



from the products of hydrolysis of silk fibroin,[1] which is identical with the synthetic compound from glycine and *d*-alanine. This diketo-piperazine corresponds to the two dipeptides *glycyl-alanine* and *alanyl-glycine*.

Glycyl-d-*alanine* is the first recorded instance of a common link between polypeptide synthesis and protein disruption.

It was isolated from the products of hydrolysis in the form of the α-naphthalene-sulphonic derivative and its structure confirmed by hydrolysing the latter to alanine and naphthalene-sulphoglycine. The compounds with naphthalene sulphonic acid are of great service in determining the structure of polypeptides.

d-*Alanyl*-l-*leucine* has been found among the hydrolytic products of elastin, and l-*leucyl*-d-*glutamic acid* among those of gliadin.

Glycyl-proline anhydride was discovered by Levene and Beatty among the products of digestion of gelatin, and Osborne and Clapp, by hydrolysing gliadin with hot sulphuric acid, observed the formation of a dipeptide of phenyl-alanine and proline. Dakin[2] has obtained an *isoleucyl-valine-anhydride* from the hydrolysis products of caseinogen. Fischer and Abderhalden also succeeded in preparing from silk fibroin a *tetrapeptide* composed of two glycine residues united with a *d*-alanine and an *l*-tyrosine residue. This compound already shows great similarity to the albumoses. An examination of the synthetic pentapeptide l-*leucyl-triglycyl*-l-*tyrosine* proved it to possess all the

[1] E. Fischer and Abderhalden, *Ber.*, 1906, 39, 752; 1907, 40, 3544. [2] Dakin, *Biochem. J.*, 1918, 12, 290.

characteristics of the albumoses, hence it is to be assumed that the latter are by no means as complex as has hitherto been supposed.

A compound of special interest is the tripeptide *glutathione* isolated by Hopkins[1] and shown to be present in the majority of animal cells. It is built up of the three amino-acids glycine, glutamic acid (p. 283) and cysteine. This tripeptide appears to function as an oxygen carrier, the mercaptan group in the cysteine unit readily becoming oxidised to a disulphide, which may again be reduced to give glutathione (compare cysteine and cystine, p. 234).

Properties of the Polypeptides

The polypeptides are solid substances which generally dissolve readily in water and very sparingly in alcohol. Mixed polypeptides as a rule dissolve more easily in water than those built up from the same amino-acid radical. The majority of the members of this group melt with decomposition at a temperature above 200°. Whereas most of the α-amino acids have a sweet taste, the polypeptides are slightly bitter (or insipid), therein resembling the natural peptones. The higher polypeptides from the tripeptides upwards are precipitated by phosphotungstic acid in sulphuric acid solution, the precipitates being generally soluble in excess of the reagent. All the ordinary polypeptides immediately develop a blue or bluish-violet colour on being boiled in aqueous solution with precipitated copper oxide. A number of them also show the biuret reaction.[2]

The amino and carboxyl groups in the polypeptides are capable of undergoing the same reactions as in the amino acids. Thus the polyglycine esters yield diazo-esters on treatment with nitrous acid:—

$$\underset{\text{Glycyl glycine ester}}{H_2NCH_2CO \cdot NHCH_2CO_2C_2H_5} \xrightarrow{HNO_2} \underset{\text{Diazo-acetylamino-acetic ester}}{N_2:CHCO \cdot NHCH_2CO_2C_2H_5}$$

Since these show the same reactivity as diazoacetic ester (p. 217), the azo group being readily exchanged for a variety of other atoms and groups, they may prove of no small importance in the future for the preparation of polypeptide derivatives.

Esters of polypeptides are much more easily purified and identified than the parent compounds, and may be used for the synthesis of more complex polypeptides. They may be prepared just as readily as those of the amino acids, by the use of alcoholic hydrochloric acid. Esters of the dipeptides are comparatively easily converted into diketopiperazines (see p. 215) on treatment with alcoholic ammonia.

[1] Hopkins, *Nature*, 1929, 445; Hunter and Eagles, *J. Biol. Chem.*, 1927, 72, 147. [2] The biuret reaction, which is characteristic of the natural peptones, consists in adding to the substance under investigation a sufficient quantity of sodium hydroxide and a few drops of dilute copper sulphate solution. The natural proteins give a blue to reddish violet colour, and the albumoses and peptones a redder tint.

The *structure of polypeptides* may be deduced from the behaviour of the compounds formed with naphthalene-sulphonic chloride When these are heated with moderately dilute hydrochloric acid, the polypeptide chain is disrupted while the more stable link between the naphthalene-sulphonic group and the amino-acid remains fast, *e g*

$$C_{10}H_7\ SO_2\ NH\ CH_2\ CO\ NH\ CH(CH_3)\ COOH + H_2O$$
$$= C_{10}H_7\ SO_2\ NH\ CH_2\ COOH + NH_2\ CH(CH_3)\ COOH$$

From the examination of more complex polypeptides it appears that this is a general method for identifying the amino acid attached to the beginning of the chain

Synthetic polypeptides may be hydrolysed in much the same way as peptones or proteins On boiling with concentrated hydrochloric acid they are completely decomposed into amino acids, but alkalis only attack them slowly, particularly at the ordinary temperature

The behaviour of polypeptides towards the digestive ferments, and above all towards the pancreatic secretions, is of special interest Fischer and Abderhalden[1] found that the action of the pancreatic juices depends partly on the nature of the amino acids present and partly on their arrangement It thus varies with the length of the chain and in a high degree with the configuration of the molecule In general only those complexes are hydrolysed which are built up from optically active amino acids occurring in nature On the other hand, up to the present, five artificial polypeptides have been tested with gastric juices without any hydrolysis having been observed

Biological confirmation of the albuminous nature of polypeptides has also been supplied by directly feeding them to dogs It was found that peptides were degraded in the animal organism in the same manner as proteins or the simple amino acids[2]

4 Hydroxy acids of the Aliphatic Series

Nomenclature—The hydroxy acids are derived from the fatty acids by replacing a hydrogen atom of the hydrocarbon radical by a hydroxyl group They are generally designated by prefixing "hydroxy" to the name of the corresponding fatty acid According to the Geneva nomenclature their names are formed by adding the syllable "ol" to that of the parent hydrocarbon, followed by the word "acid", for example, $HO\ CH_2\ COOH$ is *hydroxy-acetic acid* or *ethanol-acid* They may also be considered to be oxidation products of the polyhydric alcohols, as expressed in the above case by the term *glycollic acid*

Among the hydroxy-acids we have the same possibilities of isomerism as in the case of the chloro- and amino-acids Similarly the position

[1] *Z physiol Ch*, 1905, 46, 52 [2] Abderhalden, *Z physiol Ch*, 1906, 47, 159

of the substituent with regard to the carboxyl group is represented by the use of letters, e.g.

$$\underset{\text{Propionic acid}}{CH_3\cdot CH_2\cdot COOH} \qquad \underset{\alpha\text{-Hydroxy propionic acid}}{CH_3\cdot CH(OH)COOH} \qquad \underset{\beta\text{-Hydroxy propionic acid}}{CH_2(OH)\cdot CH_2\cdot COOH}$$

Properties.—The hydroxy acids possess the characteristics of both alcohols and acids. Thus the presence of the carboxyl group leads to the formation of salts, esters and amides, and the hydrogen of the alcoholic hydroxyl group is also replaceable by alkali metals and alkyl or acyl radicals.

$$\underset{\text{Glycollic acid}}{\begin{array}{l} COOH \\ | \\ CH_2\cdot OH \end{array}} \qquad \underset{\substack{\text{Ethyl glycollate} \\ \text{(hydrolysable)}}}{\begin{array}{l} COOC_2H_5 \\ | \\ CH_2\cdot OH \end{array}} \qquad \underset{\substack{\text{Ethylglycollic acid} \\ \text{(not hydrolysable)}}}{\begin{array}{l} COOH \\ | \\ CH_2\cdot OC_2H_5 \end{array}}$$

The strength of the fatty acids is increased by the entrance of the hydroxyl group into the molecule, the effect being the greater the closer the hydroxyl stands to the carboxyl group. This is shown by a comparison of the dissociation constants of the acids (see p. 82).

The influence exerted by the position of the hydroxyl group is also clearly illustrated in the different manner in which water is eliminated from α-, β- and γ-hydroxy acids.

α-Hydroxy acids, on being heated, lose water in such a way that two molecules of the acid interact, the hydroxyl group of each uniting with the carboxyl group of the other molecule to form cyclic double esters known as *lactides*.

$$\underset{\alpha\text{-Hydroxy-propionic acid or lactic acid}}{\begin{array}{l} \quad\ \ COOH \\ \quad\ \ \ | \\ CH_3\cdot CH\cdot OH \end{array} + \begin{array}{r} HO\cdot CH\cdot CH_3 \\ | \quad\quad\ \ \\ HOOC \quad\quad\ \ \end{array}} = \underset{\text{Lactide}}{\begin{array}{l} \quad\ \ CO\cdot O\cdot CH\cdot CH_3 \\ \quad\ \ \ | \qquad\quad\ | \\ CH_3\cdot CH\cdot O\cdot CO \end{array}} + 2H_2O$$

β-Hydroxy acids, when heated by themselves or with dilute sulphuric acid, generally decompose into water and unsaturated acids, the water being formed by combination of the hydroxyl group with the adjacent hydrogen atom in the α- or γ-position.

$$\underset{\beta\text{-Hydroxy butyric acid}}{CH_3\cdot CH(OH)\cdot CH_2\cdot COOH} = \underset{\text{Crotonic acid}}{CH_3\cdot CH:CH\cdot COOH} + H_2O$$

The *γ- and δ-hydroxy acids* readily eliminate water, even when in solution at the ordinary temperature, and are transformed into simple cyclic anhydrides called *lactones*.

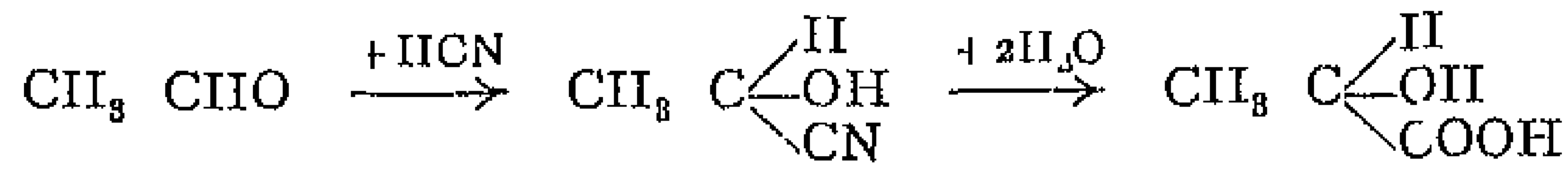
$$\underset{\gamma\text{-Hydroxy butyric acid}}{\begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO \\ | \qquad\qquad\qquad\quad\ | \\ OH \qquad\qquad\quad\ HO \end{array}} = \underset{\text{Butyrolactone}}{\begin{array}{l} CH_2\cdot CH_2\cdot CH_2\cdot CO \\ | \qquad\qquad\qquad\quad\ | \\ \underline{\qquad\qquad\qquad\quad\ } O \end{array}} + H_2O$$

Methods of Formation.—Hydroxy acids may be obtained by the following methods:—

1. From halogen-substituted fatty acids by heating with water:

$$CH_2Cl \cdot COOH + HOH = CH_2OH \cdot COOH + HCl$$

2. By the careful oxidation of polyhydric alcohols.
3. By the reduction of aldehydic or ketonic acids.
4. From amino-acids by interaction with nitrous acid (*cf.* p. 133).
5. By the addition of hydrogen cyanide to aldehydes or ketones and hydrolysis of the cyanhydrins so formed:



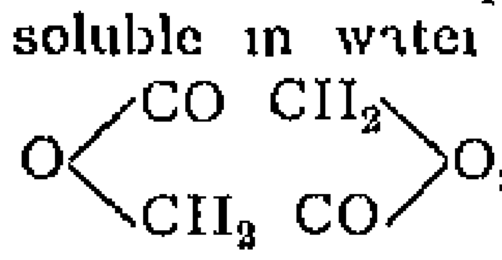
Acetaldehyde — Acetaldehyde cyanhydrin — Lactic acid

6. From fatty acids containing the tertiary CH group, by direct oxidation with permanganate:

$$\underset{\text{Isobutyric acid}}{(CH_3)_2CH \cdot COOH} + O = \underset{\alpha\text{-Hydroxy-isobutyric acid}}{(CH_3)_2COH \cdot COOH}$$

The best known and most important of the hydroxy acids are glycollic acid and ordinary or fermentation lactic acid.

Glycollic acid, *hydroxy acetic acid*, $CH_2OH \cdot COOH$, may be prepared by heating chloroacetic acid with water. It occurs in the green leaves of the wild vine and in unripe grapes. The acid forms crystals of m.p. 80°, which are readily soluble in water. When distilled *in vacuo*, water is given off and glycollide,



is produced.

Lactic Acids, $C_3H_6O_3$

Lactic acids are monohydroxy derivatives of propionic acid, $CH_3 \cdot CH_2 \cdot COOH$. It will be seen at once that two structural isomerides are possible, according as the hydroxy group occupies the α- or β-position. Of these, α-hydroxy-propionic acid or ordinary lactic acid, which exists in optically active modifications, is of special interest from the theoretical as well as the practical standpoint. The researches on the lactic acids, published in 1873 by Wislicenus, led him to the conclusion that differences between isomeric compounds having the same structural formula could only be accounted for by a different position of their atoms in space, a view similar to that advanced some time previously by Pasteur from his investigation into the tartaric acids. These two pieces of work formed the foundation of the theory of stereoisomerism put forward shortly afterwards by Le Bel and Van't Hoff independently.

Fermentation lactic acid, *ethylidene lactic acid*, *racemic α-hydroxy propionic acid*, may be obtained synthetically according to the general methods described above.

A method of practical importance consists in the "lactic fermentation" of certain substances of the sugar group, such as glucose and lactose, by means of the lactic acid bacillus The formation of lactic acid in sour milk is a consequence of this process

Buchner and Meisenheimer have shown that this action, like that of alcoholic fermentation, is caused by an enzyme produced in the living micro organism, which can be separated from the living cells without losing its activity[1]

Lactic acid is also formed from glucose, cane sugar and the pentoses by heating with caustic alkalis

Preparation of r Lactic Acid—A dilute solution of glucose is fermented by the addition of sour milk or ripe cheese, both of which are rich in lactic acid bacilli, the temperature meanwhile being maintained at 45° to 55° By keeping within these limits the danger of alcoholic or butyric fermentation is avoided As the lactic bacillus is very sensitive towards free acid, the fermentation tends to come to a stand still after a short time In order to prevent this, the lactic acid is neutralised by adding, at the beginning of the operation, milk of lime or a suspension of chalk or zinc carbonate By this means lactic acid is obtained in the form of its sparingly soluble calcium or zinc salt The calcium salt is then treated with dilute sulphuric acid, or the zinc compound with hydrogen sulphide, after which water is evaporated off and the free lactic acid obtained by distillation *in vacuo* For technical purposes the filtrate from the calcium sulphate is evaporated till the lactic acid content is about 50 per cent, and the syrupy liquid so formed is placed directly on the market

Lactic acid is used with potassium dichromate in the dyeing industry for mordanting wool, where it is of special service on account of its high solubility and lack of corrosive action It is used by tanners for removing lime from pelts, and is also employed for medicinal and domestic purposes

As may be seen from its formula, α-hydroxy-propionic acid contains an *asymmetric carbon atom* According to theory it should therefore exist in three stereoisomeric forms, viz, a dextro- and a levo rotatory modification, and a racemic inactive compound composed of equal amounts of these two (see p 34) All three forms are known The acid described above as produced by synthesis or fermentation is the racemic form, being optically inactive and capable of separation into its active components by any of the usual methods (p 39) It forms deliquescent crystals of melting-point 18°, and is readily soluble in water, alcohol and ether The zinc salt is only sparingly soluble in water, from which it separates with 3 mols of water of crystallisation

Sarco lactic acid, d *lactic acid*, or *para lactic acid* is the dextro modification of α-hydroxy-propionic acid It occurs in meat juice and is most conveniently prepared from Liebig's extract of meat It is also formed from racemic lactic acid by exposing it to the action of *Penicillium glaucum*, whereby the *l*-form is destroyed

[1] E Buchner and J Meisenheimer, *Ann*, 1906, **349**, 125

d-Lactic acid is the first recognisable degradation product of glucose, the presence of which can be traced in the body; under favourable conditions of concentration in the liver it may be reconverted into glucose. In the muscles it appears to be formed from carbohydrate-phosphoric acid compounds,[1] one of which has been isolated from fresh muscle.

l-*Lactic acid* may be obtained from the *r*-acid by resolution with strychnine, and is also formed by the action of *Bacillus acidi laevolactici* on a solution of cane sugar.

Active lactic acids differ from the racemic compound in forming a readily soluble zinc salt, crystallising with 2 mols. H_2O.

Ethylene lactic acid, *β-hydroxy-propionic acid*, *hydracrylic acid*, $CH_2OH \cdot CH_2 \cdot COOH$, is obtained from β-chloro- or β-iodo-propionic acid by warming with water and silver oxide, or from ethylene cyanhydrin, $CH_2OH \cdot CH_2CN$, by hydrolysis. It is a syrupy liquid which is readily transformed into acrylic acid, $CH_2 : CH \cdot COOH$, by elimination of water.

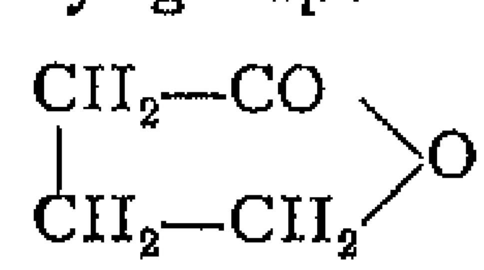
l-β-**Hydroxybutyric acid**, $CH_3 \cdot CHOH \cdot CH_2 \cdot COOH$, results in the animal organism from the degradation of fats and many amino acids (e.g. *d*-amino valeric acid, leucine). It is eliminated in large quantities in the urine in severe cases of diabetes, and its presence in the blood is characteristic of the final stages of the disease (see also p. 183). The acid forms hygroscopic crystals, m.p. 49° to 50°, and is volatile in steam, whereby it is decomposed to give water and α-crotonic acid.

Aleuritic acid, **trihydroxy-palmitic acid**, $CH_2OH \cdot (CH_2)_5 \cdot CHOH \cdot CHOH \cdot (CH_2)_7 \cdot COOH$, has been isolated as a hydrolysis product of shellac.[2]

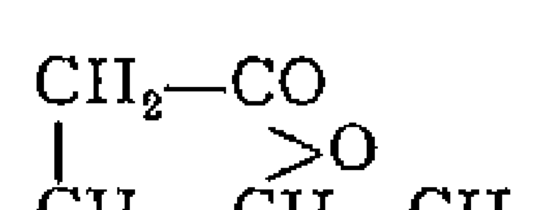
Lactones

Nomenclature.—As already stated on p. 226, the inner anhydrides of hydroxy acids, formed by splitting off a molecule of water between the carboxyl and the hydroxyl groups, are known as lactones. These anhydrides are formed particularly easily by γ- and δ-hydroxy acids, which yield γ- and δ-lactones respectively. A few α-, β- and ε-lactones are also known.

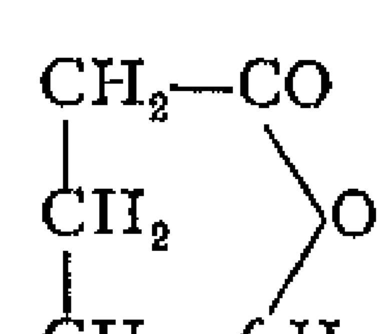
According to the Geneva nomenclature, the names of the lactones terminate in "olide," *e.g.* γ-valerolactone or 1 : 4-pentanolide. The various compounds are distinguished by use of Greek letters or numbers representing the relative positions of the carboxyl and hydroxyl groups.



Butyrolactone (Butanolide)



γ-Valerolactone (1 : 4-pentanolide)



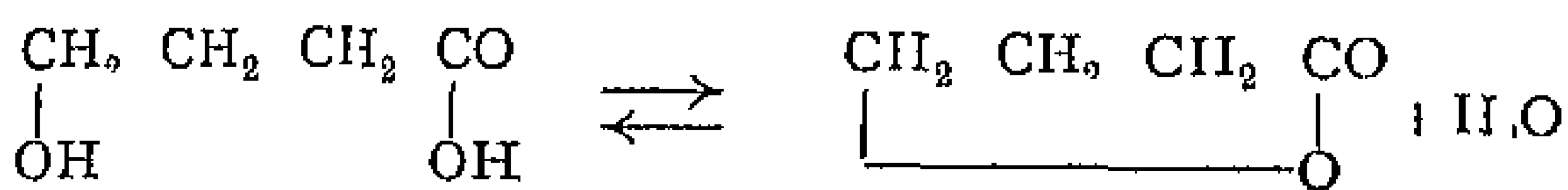
δ-Valerolactone (1 : 5-pentanolide)

Formation.—Reactions leading to the formation of lactones depend in most cases on the elimination of water from hydroxy acids, or of

[1] G. Embden and Laquer, *Z. für physiol. Chem.*, 1917, **98**, 181; G. Embden and Zimmermann, *ibid.*, 1927, **167**, 114. [2] W. Nagel, *Ber.*, 1927, **60**, 605.

hydrogen halide from halogen-substituted acids, in which the hydroxyl or halogen occupies the position corresponding to the particular lactone required

1 The majority of γ-hydroxy-acids part with water immediately at the ordinary temperature, even in aqueous solution, and cannot therefore be isolated as such But lactone formation resembles esterification in being a reversible reaction, consequently the change is never complete in the presence of water, a state of equilibrium being set up between the acid on the one hand and the lactone and water on the other

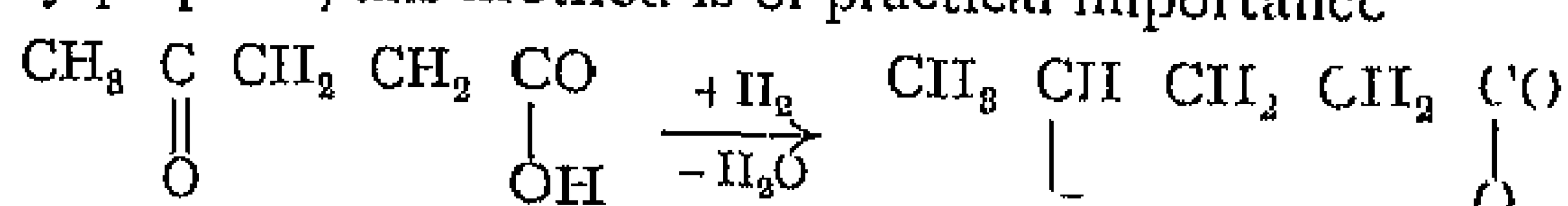


γ Hydroxy butyric acid — Butyrolactone

The introduction of substituent alkyl groups decidedly favours the formation of lactones

In order to convert the hydroxy acid into the lactone as rapidly and as completely as possible, the solution is boiled with a small quantity of hydrochloric or sulphuric acid, which brings about a marked acceleration of the change

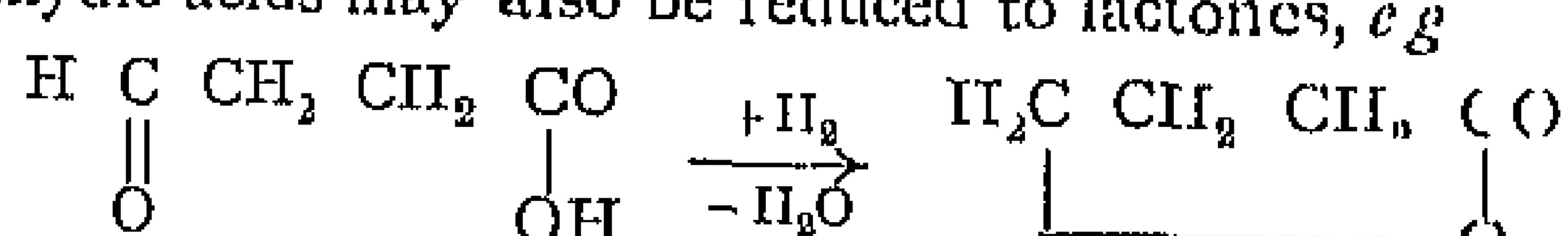
2 Ketonic acids containing the keto group in the γ- or δ-position may be converted into lactones by means of nascent hydrogen, a more or less unstable hydroxy-acid being first formed As the keto-acids are easily prepared, this method is of practical importance



Laevulinic acid — γ Valerolactone

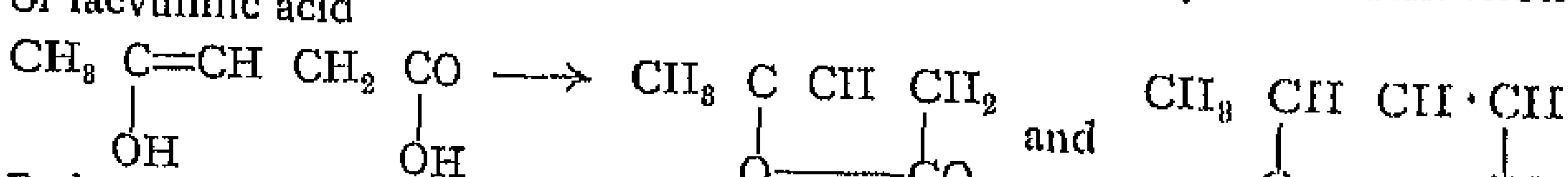
This reduction is usually carried out in alkaline solution with the aid of sodium amalgam

γ Aldehydic acids may also be reduced to lactones, *e g*



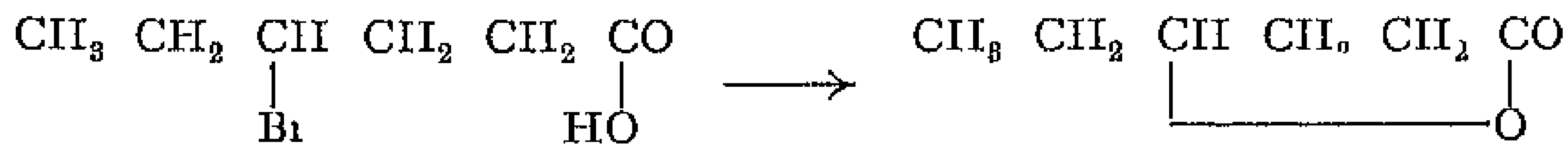
Aldehydo propionic acid — Butyrolactone

Many γ ketonic acids are directly converted into lactones by distillation, or treatment with dehydrating agents Under these conditions two structurally isomeric unsaturated lactones are usually formed which differ from one another in the position of the double bond in the lactone ring One of the best known examples of this type is the formation of two lactones of angelic acid by the distillation of laevulinic acid



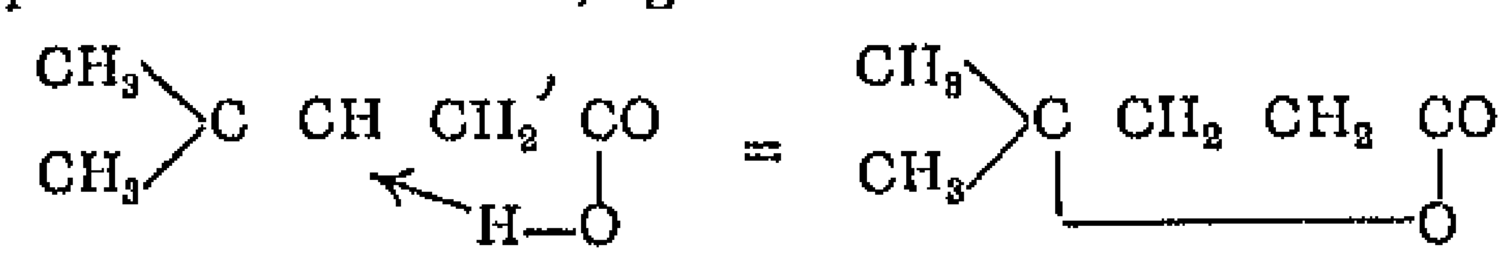
Enolic form of laevulinic acid (Hydroxy angelic acid) — α-Lactone — β-Lactone

3. γ-Halogen-substituted acids are also as a rule very unstable, and on formation they frequently undergo immediate transition into the lactone. The reactive bromo-acids are generally utilised in this method of preparation, valerolactone, for example, being formed from γ-bromo-valeric acid, and caprolactone from γ-bromo-caproic acid:



γ Bromo caproic acid — γ *n*-Caprolactone

4. Lactones may also be obtained from the unsaturated acids. In a few instances a direct rearrangement of an unsaturated acid into an isomeric γ lactone has been observed, a reaction which may be considered as the addition of the carboxyl group to the double bond, *e.g.*



Pyroterebic acid — Isocaprolactone

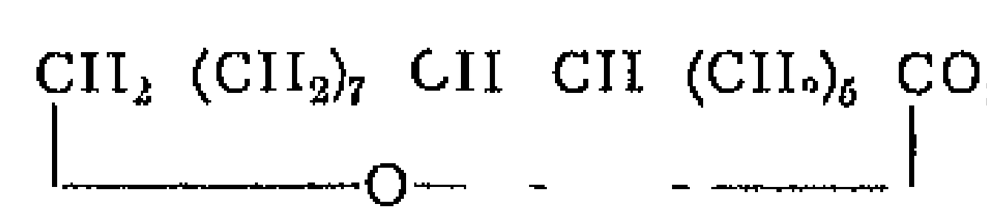
Under the influence of fuming hydrobromic acid many $\beta\gamma$ and $\gamma\delta$ unsaturated acids are converted into lactones, the unstable saturated bromo acids first formed very readily parting with hydrogen bromide.

Unsaturated acids are more conveniently converted into lactones by warming them for a few minutes with equal volumes of sulphuric acid and water.

This reaction is in every way analogous to the formation of alcohols from unsaturated hydrocarbons under the influence of aqueous sulphuric acid. In addition to these simple methods of formation, lactones may be obtained by various synthetic processes to be described later.

Certain lactones, such as *coumarin* and the *coumarins* (p. 449), are found free in nature.

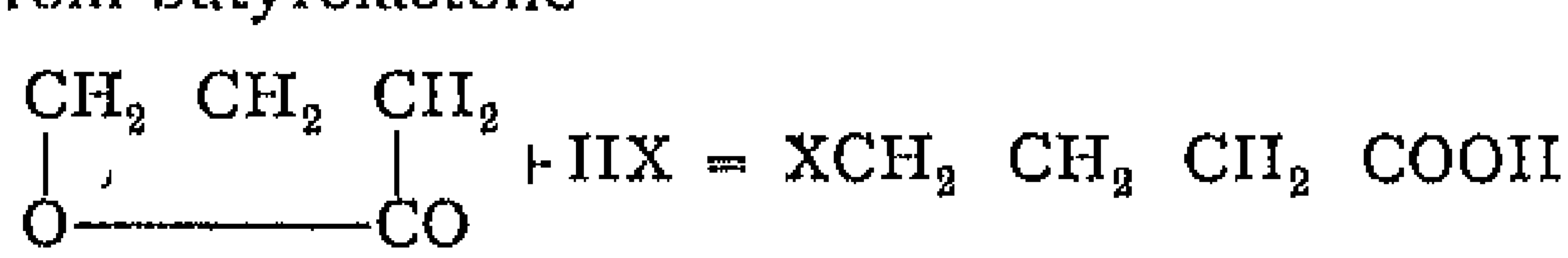
An interesting example is ambrettolide,[1]



a lactone with a 17 membered ring which is the odoriferous constituent of musk. It has been isolated from musk seed oil as a colourless viscous oil, b.p. 187° to 190° under 16 mm. pressure.

Chemical Properties.—Owing to the stability of the lactone ring, lactones have in general little tendency to enter into chemical reaction, which is not unexpected considering their nature as inner esters.

Just as water converts lactones into hydroxy-acids, treatment with hydrogen chloride, bromide or iodide converts them into halogenated acids. In this way γ-chloro-, bromo- and iodobutyric acids are readily obtained from butyrolactone:

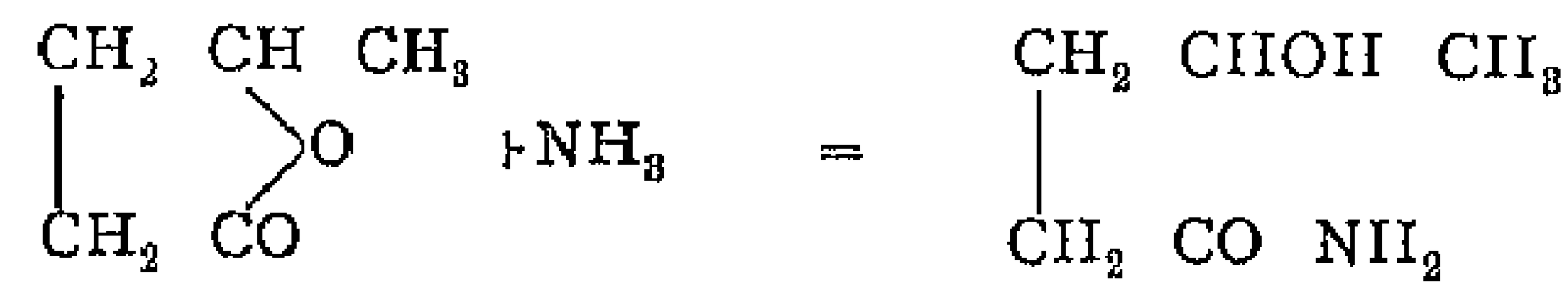


Although lactones are not attacked in the cold by alkali carbonates,

[1] M. Kerschbaum, *Ber.*, 1927, 60, 902. Compare also the investigations of Ruzicka into the constitution of civetone, *Helv. Chim. Acta*, 1926, 9, 230, 249.

they are hydrolysed like all esters by free alkalis, with the formation of salts of the corresponding hydroxy- or keto-acids [1]

Lactones also unite with ammonia, yielding amides of hydroxy-acids



and with hydrazine hydrate and phenyl hydrazine to form hydrazides

By the use of sodium amalgam in weakly acid solution, lactones of poly hydroxy acids may be reduced to the corresponding aldoses, a reaction which is of great value in the synthesis of sugars

For the action of organo magnesium halides on lactones, see Houben, *Ber*, 1904, 37, 1489

5 Hydroxy-amino Acids

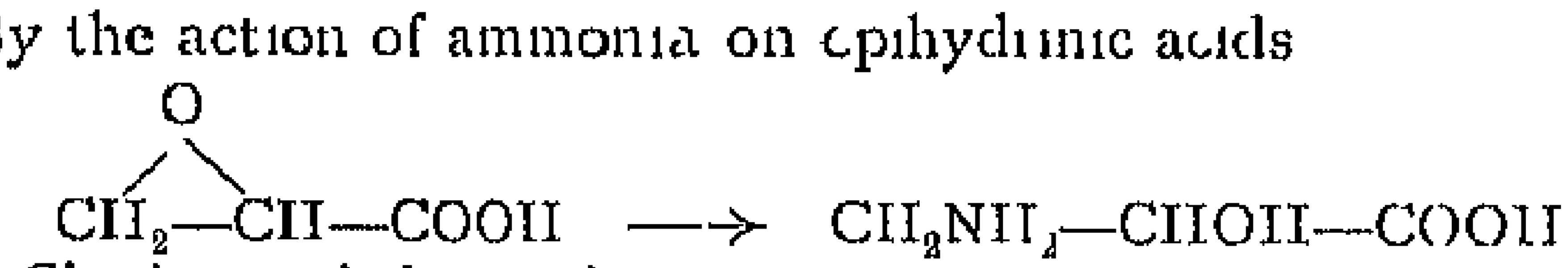
The hydroxy-amino-acids, like α-amino- and diamino-acids, are of great interest in connection with the chemistry of the proteins One of the simplest and best known examples of this type is *serine*, CH_2OH $CHNH_2$ $COOH$, which is obtained as a hydrolysis product of sericin or silk gum

Hydroxy-amino-acids are prepared by the following methods

1 By the interaction of halogen-substituted hydroxy-acids with ammonia

$$\underset{\alpha\text{-Hydroxy-}\beta\text{ chloro propionic acid}}{CH_2Cl—CHOH—COOH} \longrightarrow \underset{\alpha\text{ Hydroxy }\beta\text{ amino propionic acid}}{CH_2NH_2—CHOH—COOH}$$

2 By the action of ammonia on epihydrinic acids



Glycidic or epihydrinic acid

3 By the combined action of hydrogen cyanide and ammonia on hydroxy-aldehydes,[2] *e g*

$$\underset{\text{Glycollaldehyde ammonia}}{CH_2OH—CH(OH)(NH_2)} \longrightarrow CH_2OH—CHNH_2—CN \longrightarrow$$
$$\underset{\substack{\alpha\text{ Amino }\beta\text{ hydroxy-propionic acid}\\ \text{(Serine)}}}{CH_2OH—CHNH_2—COOH}$$

The conversion of aldol by this method into the corresponding α-amino-γ-hydroxy-valeric acid, CH_3 $CHOH$ CH_2 $CHNH_2$ $COOH$, takes place more readily than the above reaction [3]

4 By addition of hydrogen cyanide to amino-aldehydes and hydrolysis of the nitriles so formed

$$CH_2OH—(CHOH)_3—CHNH_2—CHO \longrightarrow$$
$$CH_2OH—(CHOH)_3—CHNH_2—CHOH—COOH$$

[1] See also Stobbe, *Ann*, 1902, 321, 122 [2] E Fischer and Leuchs, *Ber*, 1902, 35, 3787
[3] E Fischer, *Ber*, 1906, 39, 537

5. By the partial elimination of nitrogen from diamino-acids [1]

$$\underset{\alpha\beta\text{ Diamino propionic acid}}{CH_2NH_2—CHNH_2—COOH} \longrightarrow CH_2NH_2—CHOH—COOH$$

6. By the condensation of aldehydes with glycocoll. This method, however, is only capable of limited application [2]

7. Sorensen has developed a method of synthesising hydroxy-amino-acids which is closely related to his synthesis of diamino-acids. Thus from γ-bromo-propyl-phthalimido-malonic ester he was able to prepare α-amino-δ-hydroxy-valeric acid

$$CH_2OH\cdot CH_2\cdot CH_2\cdot CH(NH_2)COOH$$

Serine, *α-amino-β hydroxy-propionic acid*, $CH_2OH\cdot CHNH_2\cdot COOH$, was discovered in 1865 by Cramer [3] among the hydrolysis products of sericin or silk gum, and is of special interest from the chemical as well as the physiological standpoint as being the simplest and first known hydroxy-amino-acid of the aliphatic series. It was first synthesised by E. Fischer and Leuchs by method 3 above. A second synthesis, which permits of the preparation of serine from readily available starting materials, was effected by Erlenmeyer, jun. It consists in the condensation of formic ester with hippuric ester, to give *formyl-hippuric ester* I. This product is then reduced to *benzoyl-serine ester* II, which on hydrolysis with very dilute sulphuric acid yields serine, benzoic acid and alcohol

$$\begin{array}{l} HCO_2C_2H_5 \\ CH_2NH\cdot COC_6H_5 \\ | \\ CO_2C_2H_5 \end{array} \xrightarrow{-EtOH} \text{I}\ \begin{array}{l} CHO \\ | \\ CHNH\cdot COC_6H_5 \\ | \\ CO_2C_2H_5 \end{array} \xrightarrow{H_2}$$

$$\text{II}\ \begin{array}{l} CH_2OH \\ | \\ CHNH\cdot COC_6H_5 \\ | \\ CO_2C_2H_5 \end{array} \xrightarrow{H_2SO_4} \begin{array}{l} CH_2OH \\ | \\ CHNH_2 + C_2H_5OH + C_6H_5COOH \\ | \\ COOH \end{array}$$

Serine separates from aqueous solution in slender leaflets, which on rapid heating melt in the neighbourhood of 240° with evolution of gas. The acid obtained by the hydrolysis of proteins is usually completely inactive, probably owing to racemisation under the influence of the reagents employed. Resolution of the racemic form may be effected by converting it first into the p-nitrobenzoyl compound, and resolving this by crystallisation of the quinine or brucine salts. The subsequent removal of the p-nitrobenzoyl group offers no difficulty. l-Serine is the natural product as found in proteins, and has been

[1] Neuberg and Silbermann, *Ber.*, 1904, 37, 341. [2] Erlenmeyer, jun., *Ann.*, 1904, 337, 212. [3] *J. pr. Ch.*, 1865 [1], 96, 76.

isolated from silk On reduction with hydriodic acid and phosphorus, serine is converted into alanine

Isoserine, *α-hydroxy β amino propionic acid*, $CH_2NH_2 \cdot CHOH \cdot COOH$, is most conveniently prepared from β chloro lactic acid by heating with ammonia, and passes on reduction with HI and phosphorus into β amino propionic acid

Cysteine III and **cystine** IV are two acids standing in close relationship to serine

$$\text{III}\quad \begin{array}{l} CH_2SH \\ | \\ CHNH_2 \\ | \\ COOH \end{array} \qquad\qquad \text{IV}\quad \begin{array}{lcl} CH_2 & —S—S— & CH_2 \\ | & & | \\ CHNH_2 & & CHNH_2 \\ | & & | \\ COOH & & COOH \end{array}$$

Cysteine is a thio-serine and cystine the corresponding disulphide Both were first obtained in small amount by the hydrolysis of keratin (horn) According to Erlenmeyer, jun,[1] cysteine may be prepared synthetically from benzoyl serine ester by heating it with P_2S_5 and decomposing the product with concentrated hydrochloric acid On oxidation with air it is transformed into *i*-cystine The natural active cystine is formed from *l*-serine ester by treatment with PCl_5, which converts it into β chloro-α-amino-propionic ester, and warming the free acid from the latter for $1\frac{1}{2}$ hours to 100° with aqueous barium hydrosulphide Under these conditions the halogen is exchanged for —SH, yielding active cysteine, which after removal of excess hydrosulphide and addition of ammonia may be oxidised by air to active cystine[2]

The constitution of cysteine was originally confirmed by its conversion into taurine (see p 242) This relationship is also of importance in the living organism, since cysteine is the parent substance of taurine, which forms one component of an important bile acid, *taurocholic acid*, found in ox-gall Cysteine is transformed into taurine by decarboxylation followed by oxidation $HS \cdot CH_2 \cdot CH(NH_2) \cdot COOH \longrightarrow HO_3S \cdot CH_2 \cdot CH_2 \cdot NH_2$ The reversible dehydrogenation of cysteine to cystine plays an important part in the breathing processes in the tissues[3] (*cf* p 224)

Cysteine, cystine and a third amino-acid **methionine** are the only known sulphur compounds entering into protein structure Methionine has been synthesised by Barger and Coyne[4] and shown to be *γ-methylthiol-α-amino-butyric acid*, $CH_3S \cdot CH_2 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$.

[1] *Ann*, 1904, **337**, 241 [2] E Fischer and Raske, *Ber*, 1908, **41**, 893 For the preparation of cystine from wool, see A R T Merrill, *J Am C S*, 1921, **43**, 2688 [3] F G Hopkins, *Skand Arch f Physiologie*, 1926, **49**, 33 [4] Barger and Coyne, *Biochem J*, 1928, **22**, 1417 The acid was first isolated by J Mueller (*J Biol Chem*, 1923, **56**, 157)

XII

Polyhydric Alcohols

In addition to the monohydric alcohols already described (p 131), polyhydric alcohols are known containing two or more hydroxyl groups in the molecule Only in rare cases are more than one of these groups found attached to the same carbon atom Polyhydric alcohols usually undergo all the reactions quoted under monohydric alcohols, although, as would be expected, the changes suffered by the latter by virtue of the single —OH grouping may be repeated several times in the case of the polyhydric compounds Derivatives may thus be formed which, like hydroxy-acids and amino-alcohols, contain more than one typical class group in the molecule These compounds generally possess the characteristics of both of the classes they represent

I —DIHYDRIC ALCOHOLS OR GLYCOLS, AND THEIR DERIVATIVES

Dihydric alcohols take their name from glycol, the simplest member of the series, and may be derived from hydrocarbons by replacing two hydrogen atoms, attached to different carbon atoms, by hydroxyl groups They are distinguished as α-, β-, γ- or δ-glycols, according as the hydroxyl groups stand in the 1 2, 1 3, 1 4, or 1 5 positions to one another

Methods of Formation—Dihydric alcohols may be obtained in the same manner as the mono-substituted compounds from the corresponding halogen derivatives, by heating them with water or potassium carbonate, or by bringing them into reaction with silver or potassium acetate and hydrolysing the diacetates so formed This reaction is of special importance for the preparation of α-glycols, since the corresponding 1 2-dibromides are readily obtained by the addition of bromine to olefines In this way glycol was first prepared by Wurtz

$$CH_2\ CH_2 \xrightarrow{+Br_2} CH_2Br\ CH_2Br \xrightarrow{+2H_2O} CH_2OH\ CH_2OH + 2HBr$$

Other glycols may be obtained in a similar manner For example, allyl bromide combines with hydrobromic acid to form trimethylene bromide, which may readily be converted into trimethylene glycol

$$\underset{\text{Trimethylene bromide}}{CH_2Br\ CH_2\ CH_2Br} \xrightarrow{2H_2O} \underset{\text{Trimethylene glycol}}{CH_2OH\ CH_2\ CH_2OH}$$

It has already been mentioned on p 112 that α glycols are formed by the cautious oxidation of olefines with aqueous potassium permanganate They are also produced, together with secondary alcohols, when ketones are reduced electrolytically or by means of sodium Under these conditions acetone yields isopropyl alcohol and

pinacol (tetramethyl ethylene glycol, formerly known as *pinacone*). The latter on treatment with dilute sulphuric or hydrochloric acid undergoes a remarkable intramolecular rearrangement with elimination of water to form **pinacolone** (originally *pinacoline*).

$$\begin{array}{c}(CH_3)_2CO\\ (CH_3)_2CO\\ \text{Acetone}\end{array} \xrightarrow{2H} \begin{array}{c}(CH_3)_2C\cdot OH\\ | \\ (CH_3)_2C\cdot OH\\ \text{Pinacol}\end{array} \xrightarrow{-H_2O} \begin{array}{c}CH_3\cdot CO\\ | \\ (CH_3)_3C\\ \text{Pinacolone}\end{array}$$

In a similar manner, by the reduction of various ketones, a number of **tetra-alkylated ethyleneglycols** have been prepared, which are classed as **pinacols** and show the same behaviour with dilute mineral acids as pinacol itself.

More recently glycols have been obtained by the action of alkyl magnesium halides on diketones, keto alcohols, aldehydo alcohols and dicarboxylic esters. Zelinsky, for example, obtained pinacol from diacetyl and methyl magnesium iodide:

$$\underset{\text{Diacetyl}}{CH_3CO\cdot COCH_3} \xrightarrow{2CH_3\cdot MgI} \underset{\text{Pinacol}}{(CH_3)_2C(OH)\cdot C(OH)(CH_3)_2}$$

Properties.—Glycols are generally viscous, colourless and sweet-tasting liquids (hence the name), which are easily soluble in water and alcohol but difficultly soluble in ether. Their boiling-points lie considerably higher than those of the monohydric alcohols with a similar carbon chain.

The chemical behaviour of the glycols may be deduced from that of the simple alcohols. Thus the hydroxyl group may be displaced by halogen, or its hydrogen atom replaced by an alkyl or acyl group, or by an alkali metal. Primary glycols also undergo oxidation to aldehyde and acid. Since, however, we are dealing with compounds containing two hydroxyl groups in the molecule, it is obvious that all these reactions may take place in two stages, as indicated in the following formulæ:

$$\begin{array}{c}CH_2\cdot ONa\\ | \\ CH_2\cdot OH\\ \text{Monosodium}\\ \text{derivative}\end{array} \quad \begin{array}{c}CH_2\cdot ONa\\ | \\ CH_2\cdot ONa\\ \text{Disodium}\\ \text{derivative}\end{array}, \quad \begin{array}{c}CH_2\cdot OC_2H_5\\ | \\ CH_2\cdot OH\\ \text{Glycol}\\ \text{monoethyl ether}\end{array} \quad \begin{array}{c}CH_2\cdot OC_2H_5\\ | \\ CH_2\cdot OC_2H_5\\ \text{Glycol}\\ \text{diethyl ether}\end{array},$$

$$\begin{array}{c}CH_2\cdot O\cdot COCH_3\\ | \\ CH_2\cdot OH\\ \text{Glycol monoacetate}\end{array} \quad \begin{array}{c}CH_2\cdot O\cdot COCH_3\\ | \\ CH_2\cdot O\cdot COCH_3\\ \text{Glycol diacetate}\end{array},$$

$$\begin{array}{c}CH:O\\ | \\ CH_2\cdot OH\\ \text{Glycollic}\\ \text{aldehyde}\end{array} \quad \begin{array}{c}CH:O\\ | \\ CH:O\\ \text{Glyoxal}\end{array}, \quad \begin{array}{c}COOH\\ | \\ CH_2\cdot OH\\ \text{Glycollic}\\ \text{acid}\end{array} \quad \begin{array}{c}COOH\\ | \\ CH:O\\ \text{Glyoxalic}\\ \text{acid}\end{array} \quad \begin{array}{c}COOH\\ | \\ COOH\\ \text{Oxalic}\\ \text{acid}\end{array}$$

By the action of phosphorus pentachloride both hydroxyl groups are replaced by chlorine, giving the neutral hydrochloric acid esters of the glycols, *e.g.* $CH_2Cl\cdot CH_2Cl$, which may also be considered as dichloro-substitution products of the paraffins. On the other hand, when heated

with hydrogen chloride or bromide only one hydroxyl group is replaced by halogen, with the production of **chlorohydrins** and **bromohydrins**

$$\begin{array}{l} CH_2\ OH \\ | \\ CH_2\ OH \end{array} + HCl = \begin{array}{l} CH_2\ Cl \\ | \\ CH_2\ OH \end{array} + H_2O$$

Ethylene chlorohydrin

It is an easy matter to replace the halogen in these halogenohydrins by other groups such as NH_2 or SO_3H, and they are therefore utilised in preparing the majority of glycol derivatives When treated with alkalis the chlorohydrins split off hydrochloric acid to form **alkylene oxides**, which are inner anhydrides of the glycols

$$\begin{array}{l} CH_2Cl \\ | \\ CH_2OH \end{array} = \begin{array}{l} CH_2 \\ | \\ CH_2 \end{array}\!\!>O + HCl$$

Ethylene oxide

By means of dehydrating agents, such as P_2O_5 and zinc chloride, the β-, γ- and δ-glycols are also directly transformed into cyclic oxides of the same type

Ethylene glycol, *glycol*, *ethan-diol*, $CH_2OH\ CH_2OH$, is formed according to the methods already described It is an oily, colourless liquid, b p 197 5° and sp gr 1 125, which is miscible with water and alcohol but only dissolves sparingly in ether On oxidation it yields glycollic acid and finally oxalic acid

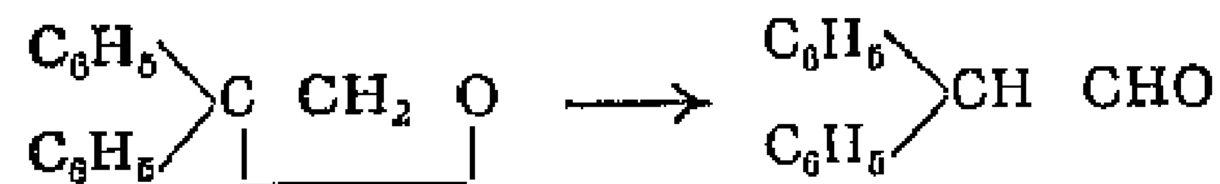
Considerable amounts of glycol are used in admixture with water, in order to prevent the latter from freezing, for a similar reason *glycol dinitrate* is sometimes added to nitroglycerin Certain ethers and organic esters of glycol, especially *glycol mono ethyl ether* and *glycol diacetate*, are employed as solvents for cellulose esters

Among the derivatives of dihydric alcohols the most important of the halogen and amino compounds are described below Oxidation products are dealt with later in another section

Glycol chlorohydrin, *ethylene chlorohydrin*, $CH_2Cl\ CH_2OH$, b p 130°, formed by leading hydrogen chloride into hot glycol, or ethylene into aqueous hypochlorous acid, is a liquid which is miscible in all proportions with water When treated with potassium cyanide it is converted into ethylene cyanhydrin, $CH_2CN\ CH_2OH$, the nitrile of ethylene-lactic acid

Ethylene oxide, $\begin{array}{l} CH_2 \\ | \\ CH_2 \end{array}\!\!>O$, is formed by distilling the chlorohydrin with sodium hydroxide It boils at 13°, possesses an ethereal smell and has a marked tendency to unite with a variety of substances, combination being accompanied by the rupture of the ring, consequently it is frequently employed as a starting material for the preparation of other compounds For example, in the presence of water it combines with ammonia and amines to form hydroxy ethylamine bases Alkylene

oxides and their substitution products may also undergo intramolecular rearrangement to yield aldehydes, *e g*,

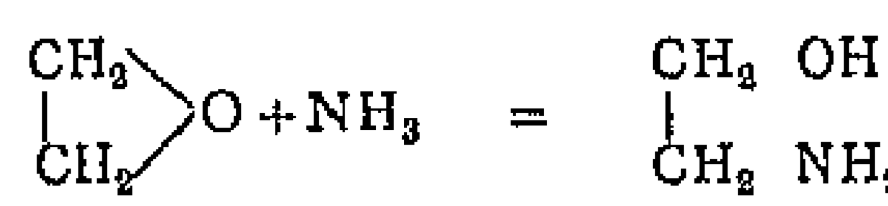


Diphenyl ethylene oxide → Diphenyl acetaldehyde

Amines derived from Dihydric Alcohols

(*a*) MONOAMINES, HYDROXY ALKYL BASES

Hydroxy ethylamine, *aminoethyl alcohol*, $CH_2OH\ CH_2NH_2$, is the nitrogenous base of many phosphatides, *e g* of the kephalins (see p 192) It is produced during the putrefaction of serine in the absence of air (under a thick layer of paraffin),[1] and is best obtained by the combination of ethylene oxide with ammonia in aqueous solution It is a viscous, strongly basic liquid, b p 171°



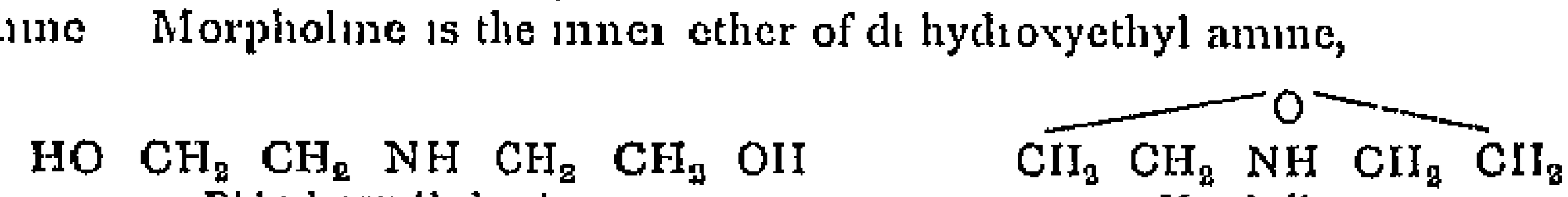
In a similar manner **di hydroxyethyl amine**, $(HO\ CH_2\ CH_2)_2NH$, and **tri hydroxyethyl amine**, $(HO\ CH_2\ CH_2)_3N$, may be prepared When primary and secondary amines are employed instead of ammonia, the reaction with ethylene oxide leads to the formation of hydroxyethyl alkylamines,[2] $HO\ CH_2\ CH_2\ NHR$ and $HO\ CH_2\ CH_2\ NR_2$ Dimethylamine, for example, reacts with ethylene oxide to form **hydroxyethyl dimethylamine**, $HO\ CH_2\ CH_2\ N(CH_3)_2$, which is of interest as being one of the fission products of the alkaloid morphine (see index)

Hydroxyalkyl amines may also be obtained by the application of the Grignard reaction to amino esters,[3] *e g*,

Glycine ester → Diphenyl hydroxyethylamine

Diethylamino acetic ester → Diethyl hydroxyethyl diethylamine

The above mentioned di hydroxyethyl amine is closely related to **morpholine**, a compound which was formerly of interest in connection with the constitution of morphine Morpholine is the inner ether of di hydroxyethyl amine,



Di hydroxyethyl amine — Morpholine

and may be prepared by heating the latter to 160° with 70 per cent sulphuric acid, in the same way as the δ glycols may be converted into their anhydrides It is a strongly basic liquid, b p 128° As will be seen later, the idea that the alkaloid morphine is derived from this substance has been abandoned

From aminoethyl alcohol it is possible to prepare **aminoethyl ether**, $NH_2\ CH_2\ CH_2\ OC_2H_5$ This is one of the simplest of the ether bases, and may be obtained

[1] F F Nord, *Biochem Zeitsch*, 1919, 95, 281 [2] The hydroxy-alkyl bases are sometimes known under the name of *hydramines*, and the hydroxy-dialkyl bases as *alkamines* [3] Paal and Weidenkaff, *Ber*, 1906, 39, 810, *cf* also *C*, 1906, I, 1584, 1586

by heating aminoethyl alcohol at 150° to 160° with concentrated hydrochloric acid, when it is converted into β-chloro-ethylamine hydrochloride; this on being further treated at 150° to 160° with a solution of sodium ethylate yields the amino ether.

$$\underset{\text{Aminoethyl alcohol}}{H_2N\cdot CH_2\cdot CH_2\cdot OH} \xrightarrow{HCl} \underset{\beta\text{-Chloro-ethylamine}}{H_2N\cdot CH_2\cdot CH_2Cl}$$

$$\xrightarrow{NaOC_2H_5} \underset{\text{Aminoethyl ether}}{H_2N\cdot CH_2\cdot CH_2\cdot OC_2H_5}$$

Aminoethyl ether is a very mobile liquid with a strong smell and an alkaline reaction. It mixes with water, alcohol and ether in all proportions, and the majority of its salts are readily soluble in water.

Dimethylaminoethyl ether, $(CH_3)_2N\cdot CH_2\cdot CH_2\cdot OC_2H_5$, is also of interest, having been isolated by Knorr as a disruption product of the alkaloids morphine, codeine and thebaine. It is formed by the interaction of dimethylamine and iodo-ether,

$$(H_3C)_2NH + I\cdot CH_2\cdot CH_2\cdot O\cdot C_2H_5 \longrightarrow \begin{matrix}H_3C\\H_3C\end{matrix}\!\!>\!\underset{H\ \ I}{N}\cdot CH_2\cdot CH_2\cdot O\cdot C_2H_5$$

or by double decomposition between chloroethyl-dimethylamine and sodium ethoxide,

$$\begin{matrix}H_3C\\H_3C\end{matrix}\!\!>\!N\cdot CH_2\cdot CH_2\cdot Cl + NaOC_2H_5 = \begin{matrix}H_3C\\H_3C\end{matrix}\!\!>\!N\cdot CH_2\cdot CH_2\cdot OC_2H_5 + NaCl$$

The base boils at 120° to 121° under 750 mm. pressure.

Closely related to hydroxyethylamine is *choline*, which is of great importance physiologically.

Choline, *hydroxyethyl-trimethyl-ammonium hydroxide*, *bilineurine*, $HO\cdot CH_2\cdot CH_2\cdot N(CH_3)_3\cdot OH$, is a compound very widely distributed in plant and animal organism, and is probably a constant product of plant life which is necessary for the building up of all plant cells. The name choline was suggested by Strecker, who discovered the substance in the bile of cattle and swine.

Choline occurs as a constituent of lecithin in the brain and in egg-yolk (see p. 192). It has been obtained as a disruption product of the alkaloid sinapine on treatment with baryta, and may also be prepared from seeds.

The constitution of choline is shown by its hydrolytic products—a concentrated aqueous solution of the substance decomposes on boiling into trimethylamine and glycol—and also by its manner of formation. It may be obtained synthetically by heating trimethylamine with ethylene chlorohydrin, or by allowing trimethylamine and ethylene oxide to react in aqueous solution at ordinary temperature.

$$\begin{matrix}CH_2\\|\\CH_2\end{matrix}\!\!>\!O + N(CH_3)_3 + H_2O = (CH_3)_3N\!\!<\!\begin{matrix}CH_2\cdot CH_2\cdot OH\\OH\end{matrix}$$

Choline is a non-crystallisable syrupy liquid, deliquescent in air and miscible in all proportions with water It has a strong alkaline reaction and little physiological activity On oxidation it is converted into betaine (see p 218)

Muscarine is the poisonous principle of the fly *Amanita muscaria*, and is closely related to choline, although its constitution is not yet established with certainty Possibly it is a dihydroxyethyl trimethyl ammonium hydroxide of the formula $(HO)_2CH\ CH_2\ N(CH_3)_3OH$

N **Dimethyl vinylamine**, $CH_2\ CH\ N(CH_3)_2$, has been obtained by the dry distillation of neurine chloride[1] It is a mobile liquid, b p 37° to 38°, which with acids is decomposed rapidly into acetaldehyde and dimethylamine It shows a great tendency to polymerise, forming a white solid mass

Neurine, *vinyl-trimethyl-ammonium hydroxide*, $CH_2\ CH\ N(CH_3)_3OH$, was discovered together with choline in 1865, by treating the brain of cattle with baryta-water It is produced during the putrefaction of choline, or on boiling the latter with baryta water Neurine is also found among the ptomaines formed by the putrefaction of proteins, particularly in dead bodies Unlike choline, to which it is so closely related in constitution, neurine is a powerful poison[2]

(*b*) Alkylene Diamines

Alkylene diamines are an interesting series of compounds which may be derived from glycols by the replacement of both hydroxyl groups by amino groups

They may be prepared synthetically by the methods used for alkyl amines (pp 158 *et seq*), *e g* by the action of ammonia on alkylene bromides, $C_nH_{2n}Br_2$, or by the reduction of alkylene cyanides,[3] $C_nH_{2n}(CN)_2$ Certain diamines are also formed during the putrefaction of flesh, etc

They are liquids or low melting solids of strong basic properties, which by loss of ammonia readily pass into cyclic imides

Ethylene diamine, $NH_2CH_2\ CH_2NH_2$, may be obtained together with other products by heating ethylene dibromide to 100° with alcoholic ammonia

$$Br\ CH_2\ CH_2\ Br + 2NH_3 = NH_2\ CH_2\ CH_2\ NH_2 + 2HBr$$

It melts at 8 and boils at 116°, and unites with water to form a hydrate of m p 10° and b p 118° When the hydrochloride of ethylene diamine is heated it is converted into piperazine

Diethylene diamine, piperazine, hexahydro-pyrazine, $NH\!\left\langle\begin{array}{c}CH_2{-}CH_2\\CH_2{-}CH_2\end{array}\right\rangle\!NH$

is also produced by the reduction of pyrazine It is a strongly basic

[1] K H Meyer and H Hopff, *Ber*, 1921, **54**, 2274 [2] For the manner in which the physiological activity of choline, neurine and allied compounds is related to their chemical constitution, compare E Schmidt, *Ann*, 1904, **337**, 37 [3] For a method of synthesising diamines by the elimination of CO_2 from diamino dicarboxylic acids and diamino monocarboxylic acids, *cf* C Neuberg, *Z physiol Ch*, **45**, 110 *C*, 1905, **II**, 463

compound, m p 104° and b p 145°, which is soluble in water Piperazine forms a readily soluble urate and was formerly used as a remedy for rheumatism and gout

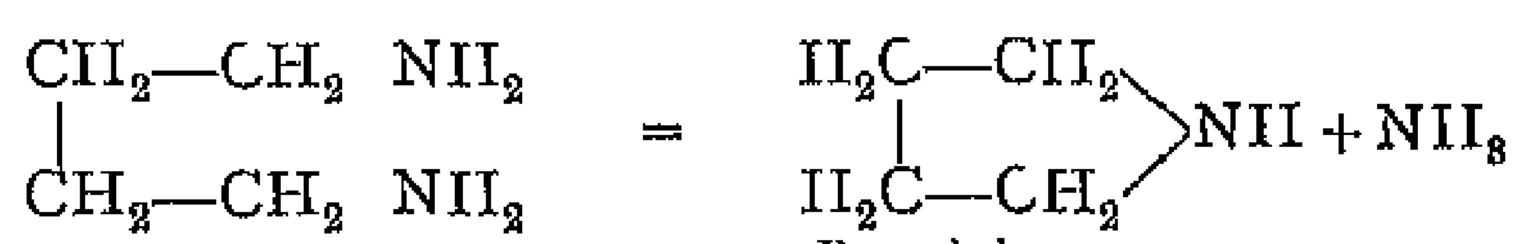
Tetramethylene diamine, *putrescine,* 1 4-*diamino-butane,*

$$NH_2\ CH_2\ (CH_2)_2\ CH_2\ NH_2$$

is formed by the putrefaction of flesh and of ornithine (see p 219) It is found together with hyoscyamine in *Hyoscyamus muticus,* and may be prepared by the reduction of ethylene cyanide,

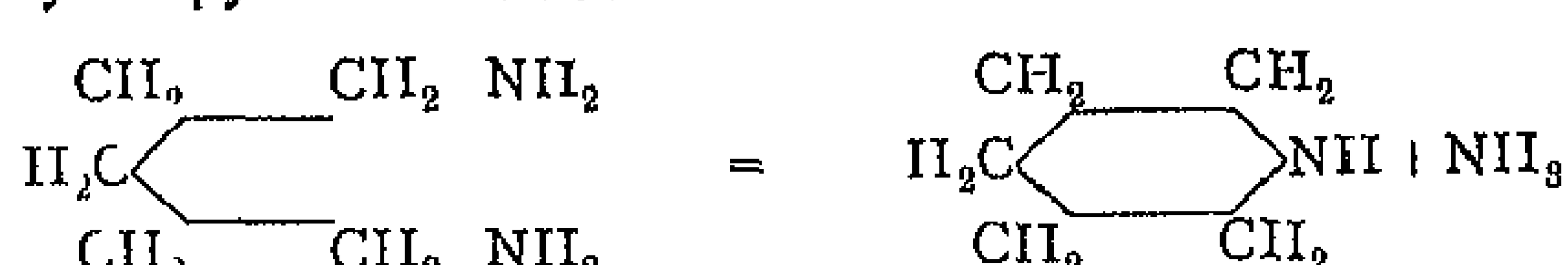
$$NC\ CH_2\ CH_2\ CN + 8H = H_2N\ CH_2\ CH_2\ CH_2\ CH_2\ NH_2$$

or better of δ phthalimido-*n*-butyronitrile[1] It melts at 27°, and when heated loses ammonia and is converted into **pyrrolidine** or *tetrahydro pyrrole*



Pyrrolidine

Pentamethylene diamine, *cadaverine,* 1 5 - *diamino - pentane,* $NH_2\ CH_2\ (CH_2)_3\ CH_2\ NH_2$, is of physiological interest, as it occurs among the products formed by the putrefaction of proteins and is therefore present in the body after death It may be obtained synthetically by the reduction of trimethylene cyanide, $CN\ (CH_2)_3\ CN$ A more convenient method is to treat benzoyl piperidine with phosphorus pentachloride and to replace the halogen atoms in the resulting 1 5-dichloro-pentane with amino groups, as indicated on p 647 This process is reversed when pentamethylene diamine hydrochloride is heated, in which case ammonia is split off and **piperidine** or hexahydro-pyridine formed



Piperidine

Taurine, *aminoethyl sulphonic acid,* $\begin{array}{l} CH_2—NH_2 \\ | \\ CH_2\ SO_3H \end{array}$ or $\begin{array}{ll} CH_2—NH_3 & \\ | & | \\ CH_2—SO_3 & \end{array}$ may be mentioned in connection with the above amino compounds It is found combined with cholic acid as *taurocholic acid* in ox-gall (hence the name taurine) and in the gall of many other animals It is best prepared from the abalone, *Haliotis,* a mollusc which occurs abundantly on the Pacific coast[2] Synthetically it may be obtained from chloroethyl sulphonic acid, $CH_2Cl\ CH_2\ SO_3H$, by treatment with ammonia It is a crystalline compound which melts with decom-

[1] W Keil, *Ber*, 1926, 59, 2816 [2] C A Schmidt and T Watson, *J Biol Chem*, 1918, 33, 499

position at 240° Nitrous acid converts it into *isethionic acid* (hydroxyethyl-sulphonic acid), $CH_2OH \cdot CH_2 \cdot SO_3H$ In the animal organism taurine is formed from cysteine by oxidation and elimination of carbon dioxide,

$$HS \cdot CH_2 \cdot CH(NH_2) \cdot COOH \longrightarrow HO_3S \cdot CH_2 \cdot CH_2 \cdot NH_2.$$

II —TRIHYDRIC ALCOHOLS

These compounds contain three hydroxyl groups attached to three different carbon atoms They may be prepared from unsaturated monohydric alcohols, either by treating with bromine and heating the resulting dibromo-alcohols with water, or by cautious oxidation with alkaline permanganate solution Their chemical character may be deduced from the presence of three alcoholic hydroxyl groups in the molecule, which can be brought into reaction individually or simultaneously to form ethers, esters and other derivatives (p 236)

Glycerol or *glycerine*, $CH_2OH \cdot CHOH \cdot CH_2OH$, is prepared technically in large quantities by the saponification of fats during the manufacture of soap and free fatty acids (p 190) It is most easily obtained in the pure state when the saponification is effected by means of steam The crude glycerol is purified by steam distillation, decolorised with animal charcoal and finally concentrated under diminished pressure

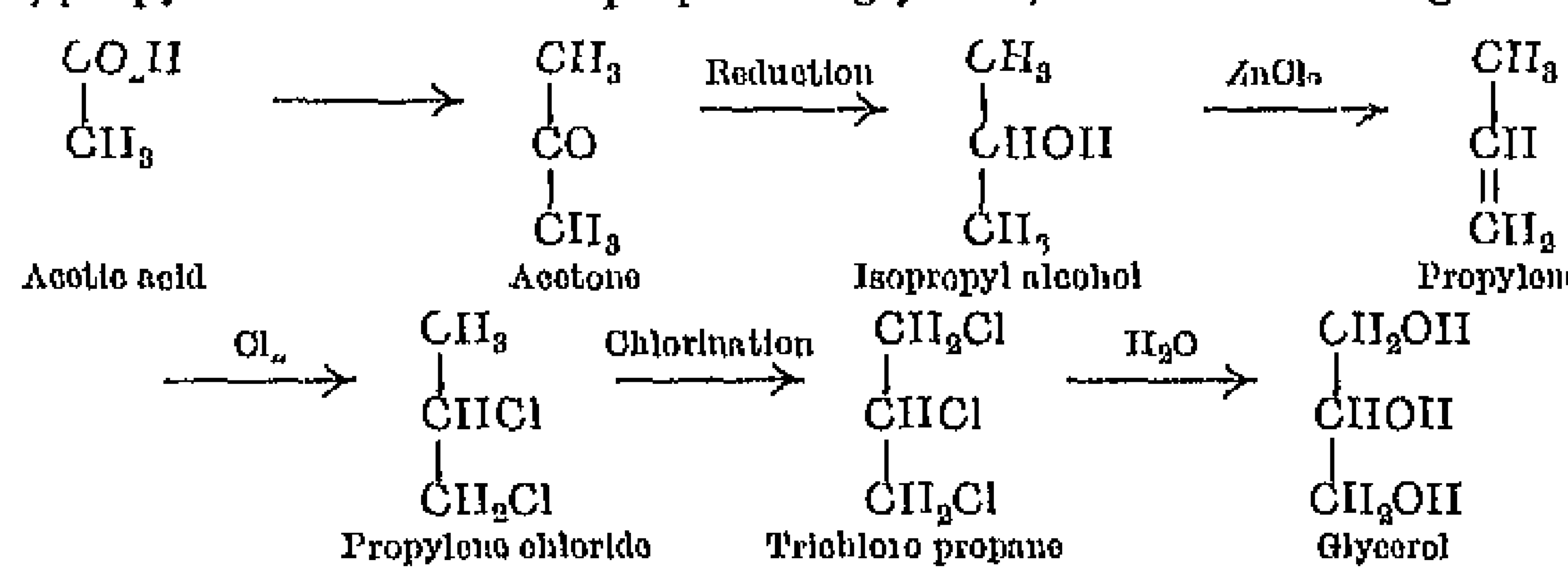
Glycerol has recently been prepared technically by a fermentation process[1] Investigation showed that the usual proportions of the products formed during the fermentation of sugar with yeast may be greatly influenced by the presence of substances of an alkaline reaction Thus the addition of salts such as disodium phosphate, sodium acetate, ammonium carbonate and sodium or magnesium bicarbonate to a 10 per cent solution of sugar, which is subsequently fermented with yeast at 30° to 35°, leads to the formation of considerable amounts of glycerol Alkaline solutions of this nature, however, provide an excellent nutrient medium for the development of all kinds of bacteria, particularly lactic bacilli These not only use up a large proportion of the sugar, but also lead to the production of impure glycerol which can only be purified with great difficulty This defect was finally overcome by employing disodium sulphite as the alkaline salt A concentration of 90 per cent sulphite (calculated with respect to the sugar) is sufficient to kill off or hinder the propagation of the lactic bacilli present, and in addition the sulphite has been found to be specifically active in the formation of glycerol With increasing proportion of sulphite the alcoholic fermentation of sugar is influenced in such a way that the production of alcohol and CO_2 diminishes, while,

[1] Connstein and Lüdecke, *Ber*, 1919, 52, 1385 C Neuberg, *Biochem Zeitsch*, 1916, 78, 238, 89, 365, 92, 234 (1918)

on the other hand, that of glycerol and acetaldehyde increases. The yield of glycerol rises from 23.1 per cent with the addition of 40 per cent Na_2SO_3 to 36.77 per cent with the addition of 200 per cent Na_2SO_3. Equally good results are obtained by the use of other sugars or of molasses, or of different types of yeast. Another advantage is that the same yeast may be used over and over again with undiminished yields, although from time to time a "recuperative" fermentation without the addition of sulphite is recommended. During the glycerol fermentation over 10 per cent of acetaldehyde is formed as a by-product. This is due to the sulphite reacting with escaping carbon dioxide to give bicarbonate and bisulphite. The latter then combines with the aldehyde to form the bisulphite compound, which is not further attacked by yeast. With the aid of this process, which can be operated without difficulty on the large scale, Germany was able to manufacture during the war more than 1 million kilograms of glycerol per month. The technical yield of glycerol amounts to 20 to 25 per cent calculated on the sugar employed.

Glycerol is also produced from sugar in the animal organism. As glycerol is an integral component of fats this explains the manner in which carbohydrates are stored up in the body in the form of fats.

A reaction of theoretical interest is the formation of glycerol from allyl alcohol by oxidation with permanganate, $CH_2:CH\cdot CH_2OH \rightarrow CH_2OH\cdot CHOH\cdot CH_2OH$. Glycerol has also been synthesised from acetic acid, which may be built up from its elements in a variety of ways, *e.g.*, acetylene + water $\rightarrow$ aldehyde $\rightarrow$ acetic acid. The acid was first converted into acetone, and thence through isopropyl alcohol, propylene and trichloro propane to glycerol, as in the following scheme:



In the pure state glycerol is a colourless viscous syrup of sweet taste (from which is derived its name) and of specific gravity 1.265 at 15°. It boils at 290° at the ordinary pressure and at 170° under 12 mm. At 0° it gradually solidifies to transparent crystals which melt at 17°. It is miscible in all proportions with water and alcohol, but is insoluble in ether. Glycerol forms soluble alcoholates with alkalis and other metallic hydroxides, and when heated with dehydrating agents yields acrolein, $CH_2:CH\cdot CHO$. As has already been seen, glycerol is the starting-point in the preparation of a number of organic compounds.

On careful oxidation with bromine or nitric acid, glycerol is converted into glycerose, the main constituent of which is *dihydroxy-acetone*, $CH_2OH \cdot CO \cdot CH_2OH$. Under the influence of dilute alkalis the latter polymerises to a sugar *acrose*, $C_6H_{12}O_6$.

Most of the glycerol manufactured is converted into nitroglycerine, but a small proportion is utilised in the preservation of such articles of food as require to be kept moist (fruits, etc.). Other uses to which it is put include the manufacture of cosmetics and skin preparations, colour printing and the production of shoe blacking.

Since a mixture of glycerol and water does not readily freeze or evaporate, it is employed in this form in gas meters and other instruments containing a liquid seal, which are necessarily exposed to extremes of temperature.

Nitroglycerine, *glyceryl trinitrate,* $C_3H_5(O \cdot NO_2)_3$, is obtained by treating glycerol with a mixture of nitric and sulphuric acids:

$$C_3H_5(OH)_3 + 3HNO_3 = C_3H_5(ONO_2)_3 + 3H_2O$$

The name nitroglycerine is misleading, as the compound it describes is no nitro compound but an ester of nitric acid, which is hydrolysed with alkalis in the normal manner to give glycerol and a metallic nitrate.

In the *preparation of nitroglycerine* pure anhydrous glycerol is added in a thin stream, with continuous stirring, to a well cooled mixture of nitric and sulphuric acids. The reaction proceeds best at 20° to 25°, and the temperature must not be allowed to rise above 30°. When interaction is complete, the stirring is discontinued and the liquid separates into two layers. The upper layer of nitroglycerine is run off into an apparatus where it is washed with water until free from acid. The lower layer consists of sulphuric acid and the excess of nitric acid; it is allowed to stand a few days, during which the last traces of nitroglycerine separate out, and after denitration is worked up for sulphuric acid.

The nitroglycerine is again washed with a solution of sodium carbonate, and finally dried by filtration through calcined soda.

In the pure state nitroglycerine is a heavy, colourless oil of sp. gr. 1.6. It has a sweet taste and is poisonous, its vapour producing headache, vertigo and loss of consciousness. It is only sparingly soluble in water but dissolves readily in alcohol, benzene and ether. At low temperatures it solidifies to needle-shaped crystals which melt at 11°.

Nitroglycerine burns quietly if ignited in small quantities, but explodes violently when rapidly heated, or on being struck or detonated with mercury fulminate. The decomposition proceeds according to the equation:

$$2C_3H_5(ONO_2)_3 = 6CO_2 + 5H_2O + 6N + O$$

In the pure state the compound is not adapted for general use as an explosive, owing to its fluid nature and extreme sensitiveness to mechanical shock. Further, the shattering rapidity with which the explosion is completed renders it useless as a propellant for artillery

In 1867 the Swedish chemist, Alfred Nobel, first showed how nitroglycerine could, by admixture with other substances, be handled and used with safety When the liquid is mixed with about one third of its weight of kieselguhr—a fine siliceous earth—it forms a plastic mass of the consistency of putty, known as **dynamite**, from which charges of definite weight are readily made In this case the kieselguhr functions merely as an indifferent medium of dilution Apparently the particles of nitroglycerine are separated from one another by the very finely divided kieselguhr, thus slowing down the speed of decomposition and allowing the effect of explosion to be calculated Further, under ordinary conditions dynamite is not liable to be exploded accidentally In some countries, notably America, wood pulp or wood powder is substituted for kieselguhr Dynamite is employed in blasting but not as a propellant for projectiles, since the walls of the gun are not capable of withstanding the sudden impulse For mining purposes in Great Britain dynamite has very largely been displaced by other mixtures, such as *blasting gelatine* (nitroglycerine with 7 to 10 per cent of collodion cotton), and *gelignite* or *gelatine dynamite*

In the year 1889 Nobel succeeded in adapting nitroglycerine for use as a *smokeless propellant powder* by mixing it with nitrocellulose (p 319) According to Nobel's process, equal parts by weight of these two substances are intimately incorporated with one another, and while the mass is still plastic it is formed into cubes, rods or other regular shapes In the product so obtained the components exist in the form of a solid solution, and as a result of the horny consistency of the material it decomposes comparatively slowly on ignition The best known nitroglycerine powder is *cordite*, composed of 65 per cent nitrocellulose, 30 per cent nitroglycerine and 5 per cent vaseline

Nitroglycerine is also utilised to a small extent in medicine for asthma, and in cases of poisoning by carbon monoxide or coal gas

III —HIGHER POLYHYDRIC ALCOHOLS[1]

A representative of the tetrahydric alcohols has long been known in **erythritol**, $CH_2OH\ \mathbf{C}HOH\ \mathbf{C}HOH\ CH_2OH$, which occurs in the free state in nature and in the form of *erythrin* (the erythritol ester of orsellinic acid) in many lichens and algæ The natural product is the inactive modification, identical with that obtained by the reduction of *d*-erythrose Erythritol forms large clear crystals of m p 120° and has a very sweet taste. It dissolves readily in water, only with difficulty in ordinary alcohol, and not at all in ether Its constitution as a normal straight chain derivative follows from its conversion into *n*-secondary butyl iodide on reduction with hydriodic acid

$$CH_2OH\ CHOH\ CHOH\ CH_2OH \longrightarrow CH_3\ CHI\ CH_2\ CH_3$$

[1] These contain asymmetric atoms, which are indicated in the formulæ by heavier type

Nitric acid converts it into the nitric ester, $C_4H_6(ONO_2)_4$, also known as *nitro-erythritol*, which like nitroglycerine is a powerful explosive. On oxidation it yields first *erythrose*, a mixture of the mono-aldehyde, $CH_2OH·CHOH·CHOH·CHO$, and the ketone $CH_2OH·CHOH·CO·CH_2OH$, and finally *erythronic acid* (trihydroxy butyric acid), $CH_2OH·CHOH·CHOH·COOH$.

Among the pentahydric alcohols or pentitols the best known representatives are **arabitol**, **xylitol** and **adonitol**. These all possess the constitutional formula $CH_2OH·CHOH·CHOH·CHOH·CH_2OH$, containing two asymmetric carbon atoms, and are stereoisomeric with one another. A homologue of this series is **rhamnitol**, $CH_3·(CHOH)_4·CH_2OH$, which is formed by the reduction of rhamnose.

Hexitols, or hexahydric alcohols, are of importance not only because they occur extensively in nature, but also on account of their close relationship to the simple class of sugars known as hexoses. The latter are aldehydes or ketones corresponding to the hexahydric alcohols, into which they may be converted by reduction with sodium amalgam. Considering their similarity in structure, it is not surprising to find that the hexitols and the hexoses possess many properties in common, such as sweet taste and solubility in water. Three alcohols of this class may be mentioned, mannitol, dulcitol and sorbitol, which are all stereoisomerides of the formula

$$CH_2OH·CHOH·CHOH·CHOH·CHOH·CH_2OH$$

Ordinary or ***d*-mannitol** occurs widely distributed in the vegetable kingdom, being found especially in manna, the evaporated sap of the manna tree. It is prepared from this source by extraction with hot alcohol and subsequent crystallisation. It is also formed during the mucous fermentation of cane sugar, and may be obtained artificially by reducing *d*-mannose or *d*-fructose with sodium amalgam:

$$C_6H_{12}O_6 + 2H = C_6H_{14}O_6$$

d-Mannitol crystallises in needles or prisms melting at 166°.

l-*Mannitol* and *i*-*mannitol* are obtained by the reduction of *l*- and *i*-mannose respectively. *i*-Mannitol was the starting point in E. Fischer's synthesis of glucose and fructose.

Dulcitol, m.p. 188°, is optically inactive and occurs chiefly in dulcite manna, from which it is prepared. It is also formed by the reduction of lactose and of *d*-galactose.

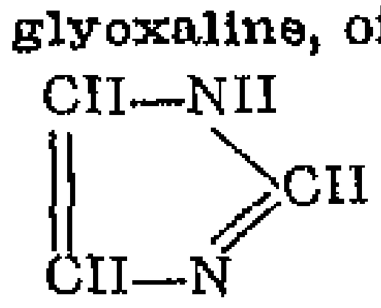
***d*-Sorbitol**, $C_6H_{14}O_6 + H_2O$, is present in the berry of the mountain ash, and is formed by the reduction of glucose, or together with mannitol from fructose. The anhydrous compound melts at 110°.

XIII

Dialdehydes and Diketones

These interesting compounds are valuable starting-points for the synthesis of various cyclic derivatives. They may be prepared by the catalytic reduction of the corresponding acid chlorides,[1] using hydrogen in the presence of finely divided palladium. Only two of the **dialdehydes**, namely glyoxal and succindialdehyde, will be dealt with here.

Glyoxal, *oxaldehyde*, *diformyl* $\begin{array}{c} H\cdot C{:}O \\ | \\ H\cdot C{:}O \end{array}$ is formed by the cautious oxidation of ethylene glycol, ethyl alcohol, or acetaldehyde with nitric acid,[2] and exists in four modifications.[3] **Poly glyoxal** $[(CHO)_2]_n$, the first of these to be known, was discovered in 1865 by Debus, and is the form obtained by the above methods of preparation. **Monomolecular glyoxal**, $CHO\cdot CHO$, was first isolated by heating poly glyoxal with phosphorus pentoxide. It is a solid which melts at 15° to a yellow liquid of b p 51°. The vapour possesses an intense emerald green colour, and on condensation yields at first a green liquid. This substance can only be preserved for a few hours, and even when kept in a strong freezing mixture rapidly polymerises to **para glyoxal**, an insoluble modification of unknown molecular weight. A solid **trimolecular form** $[(CHO)_2]_3$ has also been discovered, which in the anhydrous state is readily soluble and differs from the variety found by Debus in rapidly reducing Fehling's solution. As would be expected, glyoxal possesses a strong aldehydic character. It combines, for example, with two molecules of sodium bisulphite to give crystalline glyoxal sodium bisulphite, $C_2H_2O_2(SO_3HNa)_2+H_2O$, by means of which it is usually isolated. With concentrated ammonia glyoxal yields, among other products, a cyclic base **glyoxaline**, of the formula



which melts at 90° and boils at 263°. This is the parent substance of the *glyoxalines* or *iminazoles*, and is of importance in connection with the constitution of the alkaloid pilocarpine and of certain other natural products.

Succindialdehyde, $CHO\cdot CH_2\cdot CH_2\cdot CHO$, is formed when succindialdoxime—obtained by the interaction of pyrrole and hydroxylamine

$$\underset{\text{Succindialdoxime}}{\begin{array}{l} CH_2\cdot CH{:}NOH \\ | \\ CH_2\cdot CH{:}NOH \end{array}} + \begin{array}{l} HNO_2 \\ \\ HNO_2 \end{array} = \underset{\text{Succindialdehyde}}{\begin{array}{l} CH_2\cdot CHO \\ | \\ CH_2\cdot CHO \end{array}} + 2N_2O + 2H_2O$$

$$\underset{\text{Diallyl (1 5-hexadiene)}}{H_2C{:}CH\cdot CH_2\cdot CH_2\cdot CH{:}CH_2} \xrightarrow{\text{Ozone}}$$

$$\underset{\text{Diallyl diozonide}}{\underset{O_3}{H_2C\text{—}CH}\cdot CH_2\cdot CH_2\cdot \underset{O_3}{CH\text{—}CH_2}} \xrightarrow[\text{with water}]{\text{Heating}}$$

$$\underset{\text{Succindialdehyde}}{O{:}CH\cdot CH_2\cdot CH_2\cdot CH{:}O}$$

[1] K W Rosenmund and co workers, *Ber*, 1921, **54**, 2888, 1922, **55**, 609. [2] *Ber*, 1881, **14**, 2685. [3] Harries, *Ber*, 1907, **40**, 165.

—is treated in aqueous suspension with nitrous acid[1]; it may also be obtained from diallyl, $CH_2:CH\cdot CH_2\cdot CH_2\cdot CH:CH_2$, by treatment with ozone[2]. Diallyl is prepared by the action of sodium on allyl iodide.

From the latter reaction it follows that diallyl is 1 : 5-hexadiene.

The *diacetal of succindialdehyde* is produced during the electrolysis of the potassium salt of β-diethoxy-propionic acid,

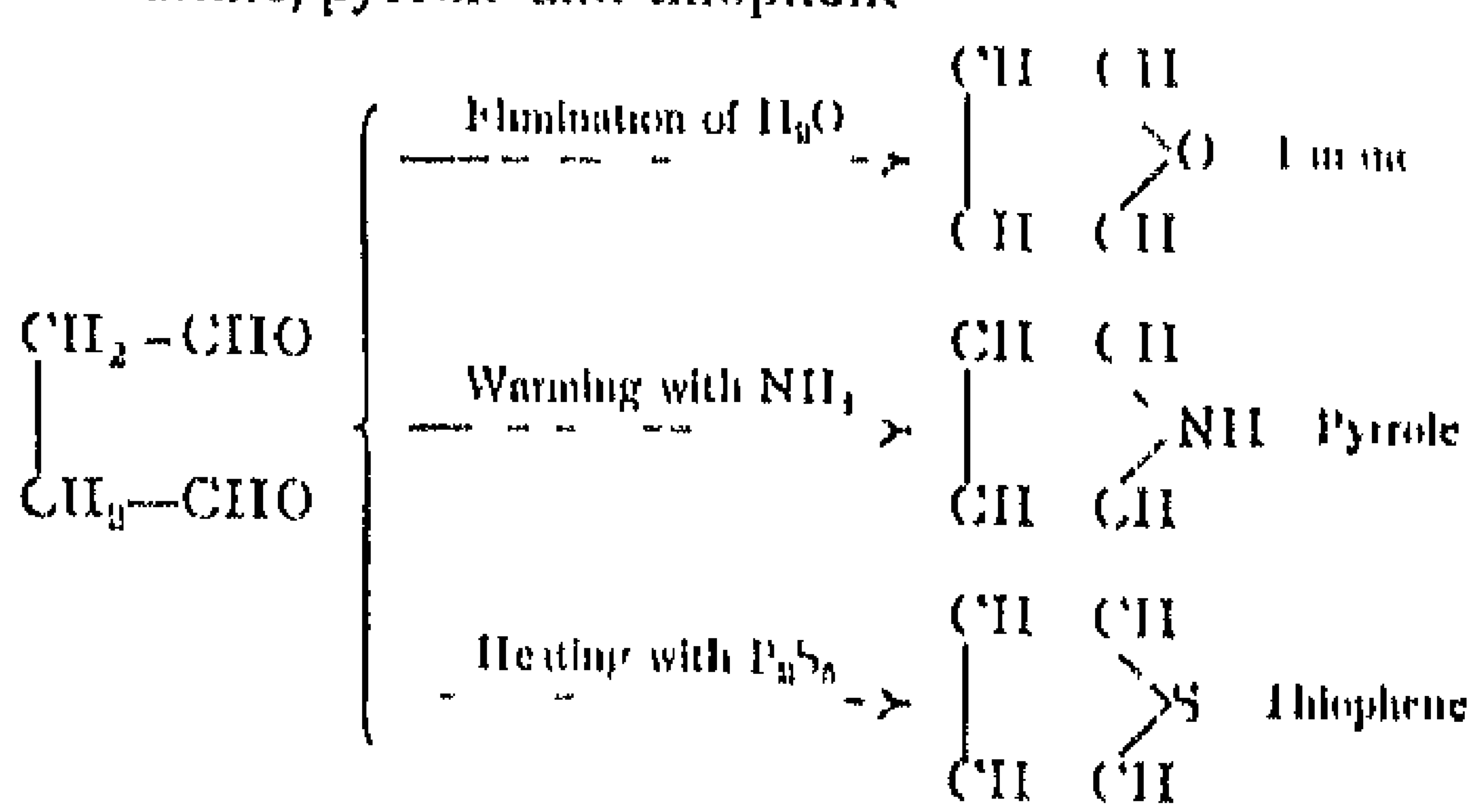
$$\begin{array}{l} K|O\cdot CO\cdot CH_2\cdot CH(OC_2H_5)_2 \\ K|O\cdot CO\cdot CH_2\cdot CH(OC_2H_5)_2 \end{array} + 2H_2O \rightarrow$$

$$\underbrace{\begin{array}{l} CH_2\cdot CH(OC_2H_5)_2 \\ | \\ CH_2\cdot CH(OC_2H_5)_2 \end{array}}_{\text{Diacetal of succindialdehyde}} + 2KOH + 2CO_2 + H_2$$

On hydrolysis, the acetal yields the free dialdehyde.

Succindialdehyde exists in a monomolecular liquid form and in a polymeric vitreous modification. The former is a colourless oil which boils at 56° under 8·5 mm. pressure, and very readily undergoes polymerisation.

By means of succindialdehyde it is possible to pass in a simple manner from an aliphatic compound to the three typical heterocyclic compounds furane, pyrrole and thiophene.



For an example of its use in synthesising still more complex heterocyclic compounds, see *tropinone*, p. 689 (R. Robinson, *J. C. S.*, 1917, **111**, 762).

DIKETONES.

Nomenclature.—According to the relative positions of the >CO groups, these compounds are distinguished as α- or 1 : 2-diketones containing the group $CO\cdot CO$, β- or 1 : 3-diketones containing the group $CO\cdot CH_2\cdot CO$, γ- or 1 : 4-diketones containing the group $CO\cdot CH_2\cdot CH_2\cdot CO$, and so on. In some cases names are also in common use which represent α-ketones as formed by the union of

[1] C. Harries, *Ber.*, 1901, **34**, 1488; 1902, **35**, 1183; 1906, **39**, 3670; 1908, **41**, 909. [2] Harries, *Ann.*, 1905, **343**, 311.

two acid radicals R CO—, and β-ketones as acyl-substituted ketones, *e g* diacetyl, $CH_3\ CO\ CO\ CH_3$, and acetyl-acetone, $CH_3\ CO\ CH_2\ CO\ CH_3$

According to the Geneva nomenclature, the diketones are named after the corresponding hydrocarbon by adding the termination -dione, *e g* acetyl-acetone or 2 4-pentane dione

1 α- or 1 2-Diketones

The α-diketones are yellow, volatile liquids of pungent smell, which are obtained from their monoximes, the isonitroso-ketones, by boiling with dilute sulphuric acid [1] *Isonitroso-ketones* are prepared by the action of nitrous acid on ketones

$$\underset{\text{Methyl ethyl ketone}}{CH_3\ CO.CH_2\ CH_3} \xrightarrow{HNO_2} \underset{\substack{\text{Isonitroso methyl ethyl ketone}\\ \text{(Diacetyl monoxime)}}}{CH_3\ CO\ C(NOH)\ CH_3}$$

$$\longrightarrow \underset{\text{Diacetyl}}{CH_3\ CO\ CO\ CH_3}$$

α-Diketones condense with *o*-phenylene diamines according to the equation

$$C_6H_4\left\langle\begin{matrix} NH_2 \\ NH_2 \end{matrix}\right. + \begin{matrix} O{=}C\ R \\ | \\ O{=}C\ R \end{matrix} = C_6H_4\left\langle\begin{matrix} N{=}C\ R \\ \quad | \\ N{=}C\ R \end{matrix}\right. + 2H_2O$$

to form cyclic compounds known as *quinoxalines*

With hydroxylamine the α diketones yield monoximes (isonitroso ketones) as well as dioximes (*glyoximes*) Phenyl hydrazine forms monohydrazones and dihydrazones, the latter also being known as *osazones*, e g

$$\begin{matrix} CH_3\ C\ N\ NH\ C_6H_5 \\ | \\ CH_3\ C\ N\ NH\ C_6H_5 \end{matrix} \quad \text{Diacetyl osazone}$$

Diacetyl, *diketo-butane*, $CH_3\ CO\ CO\ CH_3$, is obtained by the method described above [2] It is a yellow liquid of penetrating smell and b p 88°, the vapour of which possesses the colour of chlorine With hydrogen peroxide it is readily decomposed into two molecules of acetic acid

$$CH_3\ CO\ CO\ CH_3 + HO\ OH = 2CH_3\ CO\ OH$$

Diacetyl, like the simple aldehydes and ketones, is readily reduced by biochemical means, *e g* in the presence of fermenting yeast In this case *l*-rotatory 2 3-butylene-glycol is obtained [3]

Diacetyl dioxime, dimethyl glyoxime, $CH_3\ C(NOH)\ C(NOH)\ CH$ is conveniently prepared by the action of hydroxylamine on the monoxime, formed as described above from methyl ethyl ketone and

[1] For further methods of preparation, see Pauly, *Ber*, 1901, 34, 2092 Tschugaeff, *Ber*, 1907, 40, 186 [2] Diels, *Ber*, 1907, 40, 4336 [3] C Neuberg and F F Nord, *Ber*, 1919 52, 2248

nitrous acid[1] It gives a dark red precipitate with solutions of nickel salts, and is used for the qualitative and quantitative determination of this metal

2 β- or 1 3 Diketones

Preparation —β-Diketones are usually obtained by the condensation of esters with ketones, a reaction of general application discovered by Claisen It should be noted that esters can also be condensed with esters, in which case β-ketonic esters of the general formula R CO CH_2 COOR are obtained This reaction, known as the *Claisen condensation*,[2] involves the elimination of alcohol between the group R $COOC_2H_5$ of an ester and the CH_3 CO— of a ketone (or the R CH_2 CO— of a second ester molecule), and may be effected by means of the following reagents 1 an alcoholic solution of sodium ethoxide, 2 alcohol-free sodium ethoxide, 3 metallic sodium, or 4 sodamide The classical prototype of this condensation is the conversion of ethyl acetate into aceto-acetic ester, and the course of the reaction will be discussed under this substance

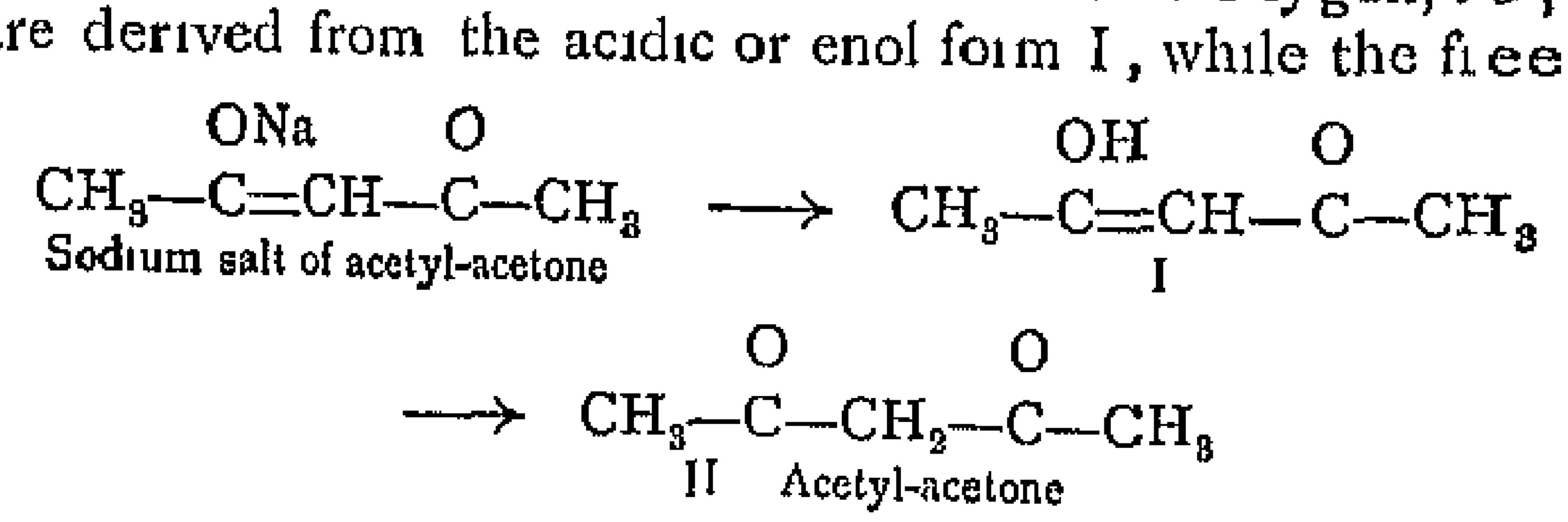
Acetyl-acetone, CH_3 CO CH_2 CO CH_3, is prepared by condensing acetic ester with acetone in the presence of one of the above agents,[2] *e g* metallic sodium The sodium salt of acetyl-acetone so obtained is then converted into the insoluble copper salt, from which the free ketone is liberated by treatment with dilute sulphuric acid.

$$\underset{\text{Acetic ester}}{CH_3\ CO\ OC_2H_5} + \underset{\text{Acetone}}{H_3C\ CO\ CH_3}$$
$$\longrightarrow CH_3\ C(ONa)\ CH\ CO\ CH_3 \longrightarrow \underset{\text{Acetyl acetone}}{CH_3\ CO\ CH_2\ CO\ CH_3}$$

It is a colourless, pleasant-smelling liquid, b p 137° When boiled with water it decomposes into acetone and acetic acid

$$CH_3\ CO\ CH_2\ CO\ CH_3 + HOH = CH_3\ CO\ CH_3 + CH_3\ COOH$$

Constitution and Properties of the β-Diketones —The β-diketones possess an acidic character as shown by the formation of metallic derivatives, many of which are insoluble in water but soluble in benzene, chloroform and other organic solvents Characteristic copper salts are also formed which are only sparingly soluble in water. In general it is assumed that the metal is united to oxygen, *i e*, that the salts are derived from the acidic or enol form I, while the free ketones

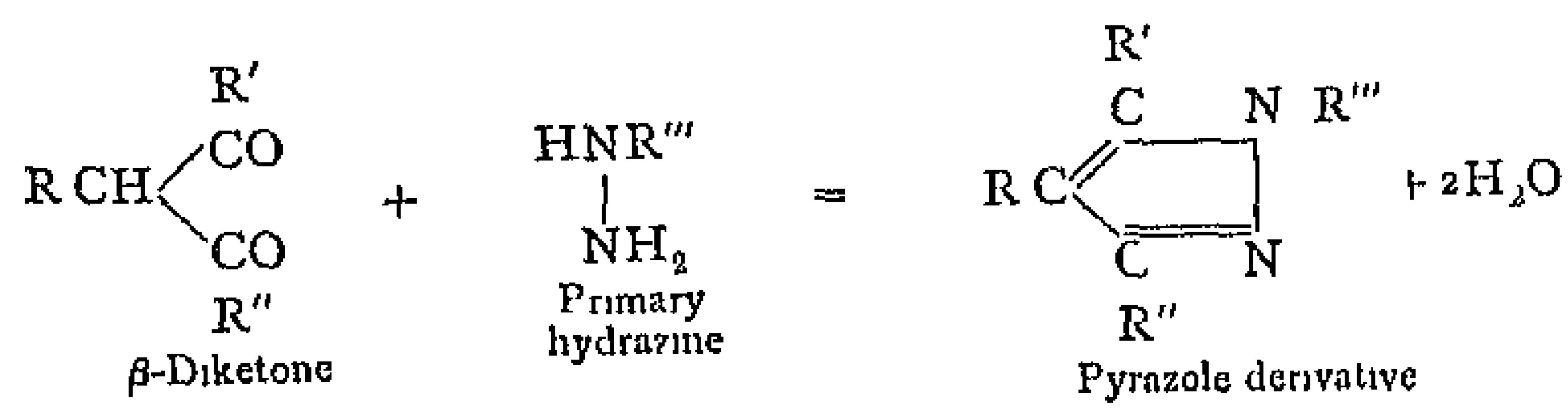


[1] *J pr Ch* (2), 1908, 77, 414 *C*, 1919, III, 43 W I Semon, *J Am C S*, 1925, 47, 2033 [2] Claisen, *Ber*, 1889, 22, 1009, 1905, 38, 709

may represent equilibrium mixtures of the keto and enol forms (*cf* p 69), although they are usually written as diketo-compounds II

The *enol form of acetyl-acetone* I has been isolated in the pure state by crystallising the equilibrium mixture from petroleum ether at a low temperature[1] A more convenient method of preparation is to distil the mixture from a glass flask,[2] when the traces of alkali from the glass catalytically convert the greater part of the keto into the enol form The distillate contains about 99 per cent enol form

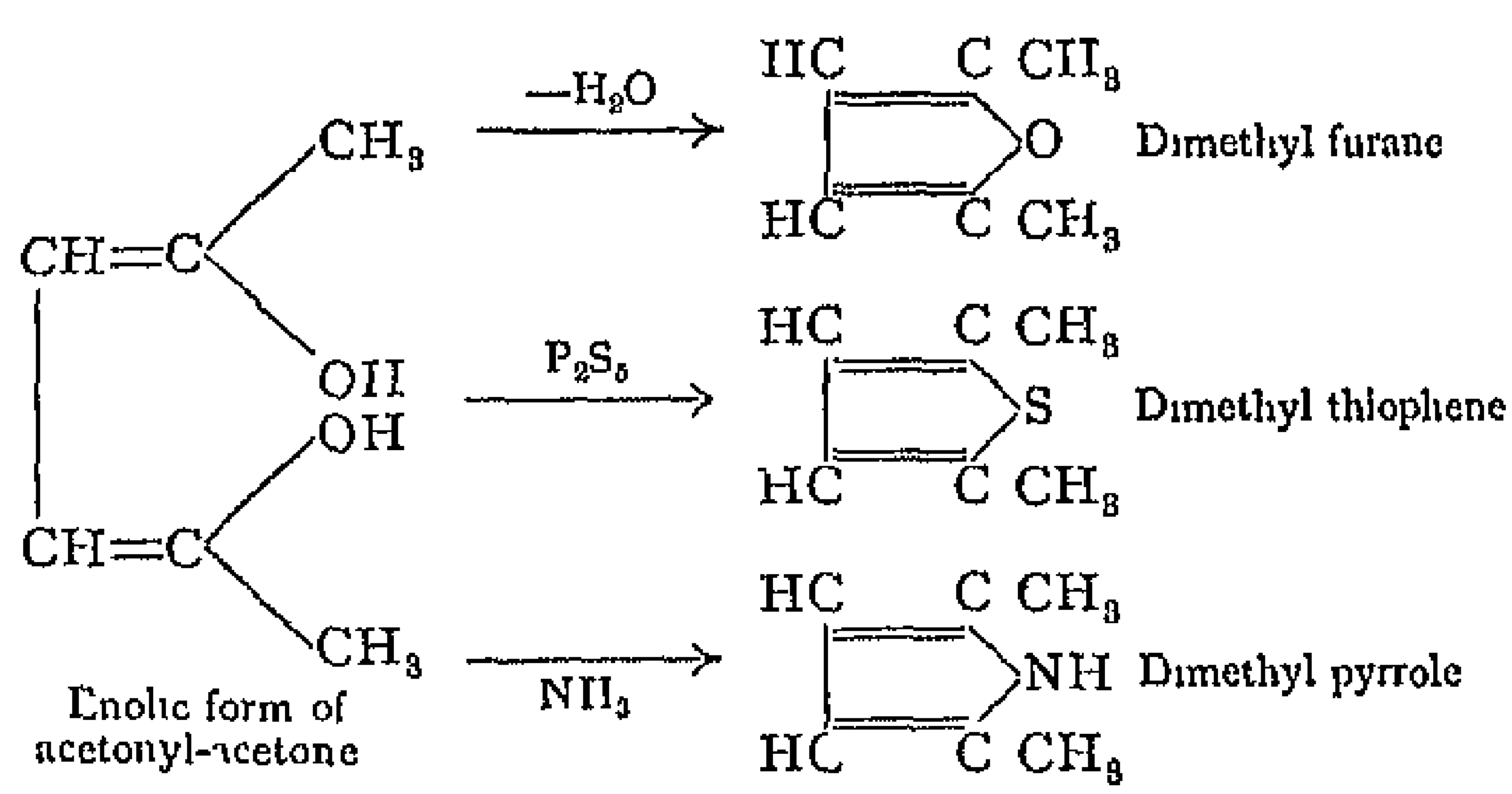
Among the great number of condensations undergone by β-diketones, one deserving special mention is their reaction with hydrazines to give *pyrazole derivatives* This reaction is the most useful of all methods for the preparation of pyrazoles, and may be formulated as follows



3 γ- or 1.4 Diketones

A compound of this type is **acetonyl acetone**, 2 5-*hexane-dione*, CH_3 CO CH_2 CH_2 CO CH_3, which is conveniently prepared from β-diaceto-succinic ester by boiling with sodium hydroxide It is a clear, pleasant-smelling liquid, b p 191° under 750 mm, which dissolves readily in water, alcohol and ether

The γ *diketones* are characterised by the ease with which they are converted into derivatives of furane, thiophene and pyrrole



Many pyrrole derivatives have the property of colouring a pine shaving intensely red, a reaction which has been proposed as a test for 1 4 diketones L Knorr[3] recommends the following procedure a small amount of the substance to be

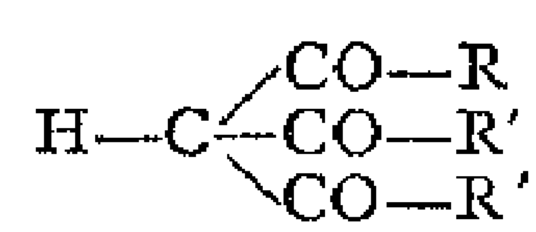
[1] L Knorr and H Fischer, *Ber*, 1911, **44**, 2771 [2] K H Meyer and Hopff, *Ber*, 1921, **54**, 579 [3] Knorr, *Ber*, 1886, **19**, 46 See also C Neuberg, *C*, 1904, **II**, 1435

tested is dissolved in glacial acetic acid, a solution of ammonia in excess of acetic acid is added and the mixture boiled for about half a minute, after which it is treated with dilute sulphuric acid and again boiled while a splint of pinewood is held in the vapour. An intense reddening of the splint shows the presence of a 1 4 diketone in the solution. Since, however, this colour reaction may be brought about by other compounds besides pyrroles, it should be used with caution.

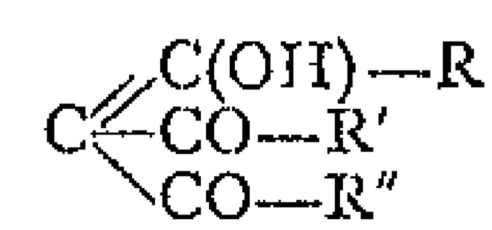
Tautomerism of the Triketones

As will be seen later in the case of aceto-acetic ester, those compounds containing the group CO CH_2 CO react on the one hand as if this group were actually present, and on the other as though they contained the complex C(OH) CH CO. In other words, they behave at times as genuine ketones and at others as enolic or *aci*-ketones. In the case of the β-diketones discussed above, no representative of the class has so far been isolated in both forms.

The triketones, however, are capable of existing in the free state in the keto form (I) as well as in the enol form (II), as has been shown by the investigations of Claisen.[1]

I 

Keto form (β)

II 

Enol or *aci* form (α)

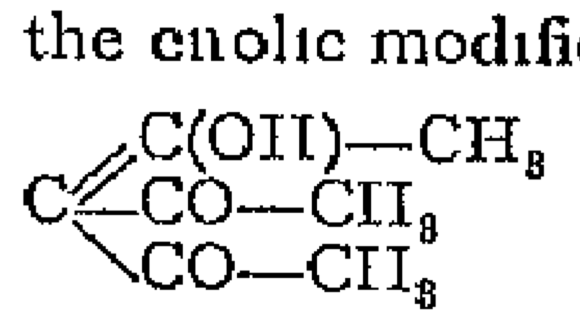
From the above formulæ, it may be seen that this peculiar form of isomerism (tautomerism) depends only on the movement of a hydrogen atom within the molecule. The compounds are therefore very labile, and it has not been found possible to prove the existence of both types in all substances of this class.

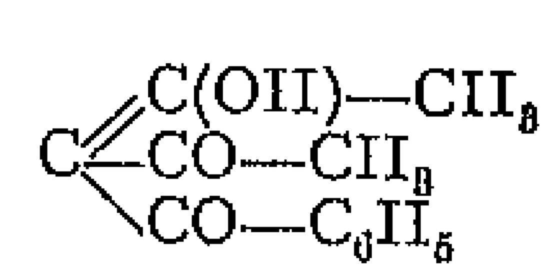
Claisen has suggested that the tendency to give the enol form increases as the acyl groups attached to the methane carbon atom become more numerous or more acidic in character. Since the acetyl group, CO CH_3, is more acidic than the benzoyl group, COC_6H_5, it should be found that in the series

$$CHA_3,\ CHA_2B,\ CHAB_2,\ CHB_3$$

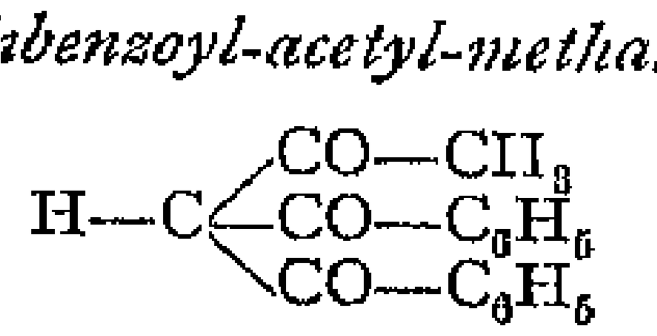
(A = acetyl, B = benzoyl) the tendency towards the enol form should steadily diminish.

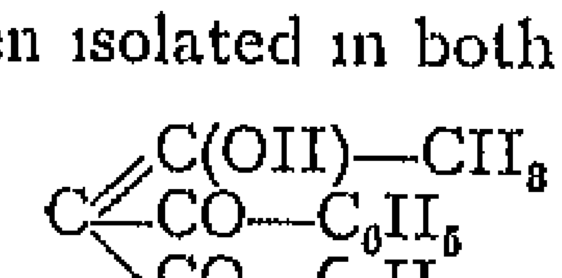
In actual fact *triacetyl-methane* and *diacetyl-benzoyl-methane* are only known in the enolic modifications,





whereas *dibenzoyl-acetyl-methane* has been isolated in both forms





[1] *Ber*, 1894, 27, 114, *Ann*, 1896, 291, 25. Claisen and Haase, *Ber*, 1903, 36, 3674.

In *tribenzoyl-methane* the α- or enolic form has already become so labile as to transform itself with extraordinary ease into the β- or keto compound

The degree of stability of the two forms of a triketone depends therefore on the nature of the acid radicals present

In the case of the triketones, Claisen was also able to show how the keto and enol (*aci*-ketonic) forms differ in chemical behaviour

The genuine ketones I are indifferent towards alkalis and ferric chloride, neither dissolving in the former nor giving any colour with the latter

The enols, on the other hand, are directly soluble in alkalis with the formation of salts They also give intense colorations with ferric chloride, a reaction which is sometimes a convenient means of rapidly distinguishing between keto and enol forms, and of following experimentally the transformation of the one into the other

The conversion of the keto into the enol form is brought about by treatment with alkalis In the presence of solvents, or in the fused state, either form is converted into an equilibrium mixture of isomerides in which the relative proportion of the two forms depends on various factors, such as the nature of the solvent and the temperature

XIV

Monobasic Aldehydic and Ketonic Acids

These acids may be regarded as oxidation products of the hydroxy acids (see p 225) and might have been treated in connection with the latter In the case with which they are converted into cyclic derivatives, however, and in the frequent occurrence of isomerism, they show many resemblances to dialdehydes and diketones, and it is more convenient to discuss them at this stage As might be expected, these acids possess the dual character of carboxylic acids and of aldehydes or ketones

Glyoxalic acid, *glyoxylic acid*, CHO COOH $+ H_2O$, is the best known aldehydic acid It occurs in young plants and unripe fruit (*e g* gooseberries and currants), and can be formed by the oxidation of ethyl alcohol with nitric acid It may be obtained synthetically from dichloroacetic acid by heating with water As in the similar case of chloral hydrate, it is assumed by many chemists that glyoxalic acid exists in chemical combination with the molecule of water which it contains according to the above formula, and thus possesses the structure of dihydroxyacetic acid, $CH(OH)_2$ COOH In this connection Debus, who discovered the compound, proposed the retention of the formula CHO COOH $+ H_2O$ as being sufficient to explain all its properties Glyoxalic acid gives the usual reactions of aldehydes,

reducing ammoniacal silver solutions, combining with sodium bisulphite, and forming an oxime When boiled with alkalis it yields glycollic acid and oxalic acid

$$2\begin{array}{l}COOH\\ |\\ CHO\end{array} + H_2O = \begin{array}{l}COOH\\ |\\ CH_2OH\end{array} + \begin{array}{l}COOH\\ |\\ COOH\end{array}$$

Formyl-phenylacetic ester is obtained by the condensation of ethyl formate with phenylacetic ester[1]

$$\underset{\text{Ethyl formate}}{H\ CO\ OC_2H_5} + \underset{\text{Phenylacetic ester}}{CH_2(C_6H_5)\ COOC_2H_5}$$
$$\longrightarrow \underset{\text{Formyl phenylacetic ester}}{H\ CO\ HC(C_6H_5)\ COOC_2H_5} + C_2H_5OH$$

This compound undergoes interesting desmotropic changes similar to those observed in the case of diketones and ketonic esters (see diaceto-succinic ester)

The isomerism of formyl-phenylacetic ester, the first case of desmotropy to be discovered, is also typical of analogous formyl compounds In addition to an oily enolic form (α-form, I) which gives rise to salts, there is a crystalline modification, which is at present believed to be an aldo enolic form (γ-form, II) The latter compound also dissolves rapidly in alkalis, but the salts produced are of the α-form No isomeric salts of formyl-phenylacetic ester are known Between the aldo-enolic and the pure enolic forms stand intermediate mixtures of lower and variable melting-point, *e g* the β-form In benzene and other indifferent solvents the aldo enolic form is slowly but completely transformed into the enolic form When dissolved in alcohols both modifications are converted into an equilibrium mixture of the purely enolic form and the purely aldehydic form (III), which at high dilutions contains a large proportion of the latter As yet the purely aldehydic or aldo form has not been isolated If the enolic hydrogen atom of the enol form is replaced by acyl groups, the derivatives obtained exhibit geometrical isomerism

$$\begin{array}{ccccc}
\begin{array}{c}CH\ (OH)\\ \|\\ C_6H_5\ C\ COOC_2H_5\end{array} & \begin{array}{c}\longrightarrow\\ \longleftarrow\end{array} & \begin{array}{c}CH\ O\\ |\\ C_6H_5\ CH\ COOC_2H_5\end{array} & \begin{array}{c}\longrightarrow\\ \longleftarrow\end{array} & \begin{array}{c}CH\ O\\ |\\ C_6H_5\ C\ C(OH)\ OC_2H_5\end{array}\\
\text{Enol form }(\alpha) & & \text{Aldo form} & & \text{Aldo-enolic form }(\gamma)\\
 & & \text{(only in alcoholic solution)} & & \\
\text{I} & & \text{III} & & \text{II}
\end{array}$$

Ketonic acids are of more importance than aldehydic acids Like the diketones (p 248) they are distinguished as α-, β-, γ- or δ-keto-acids according to the position of the —CO group with regard to the carboxyl They are generally named as acyl-substituted fatty acids,

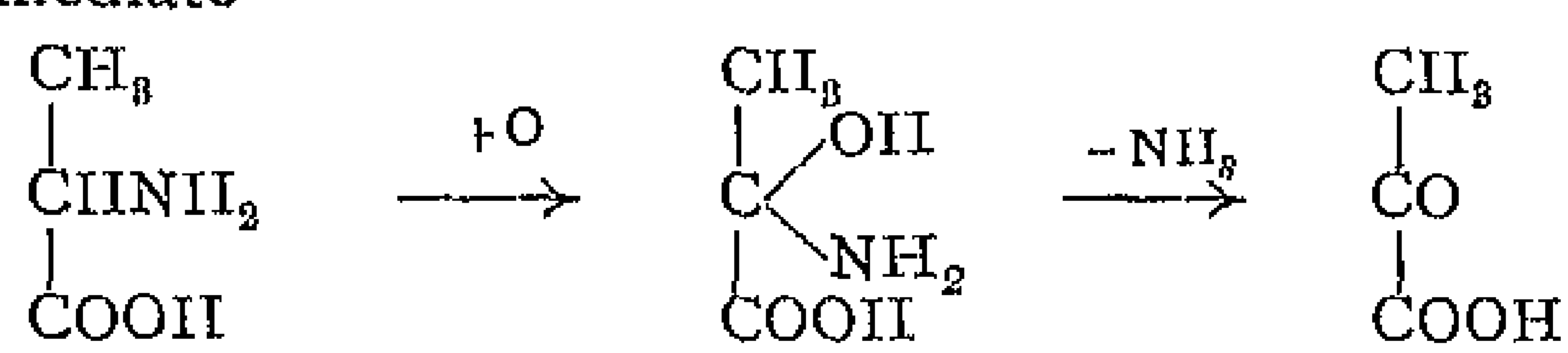
[1] Wislicenus, *Ann*, 1896, 291, 147, 1912, 898, 265

or after the Geneva nomenclature by adding the word "acid" to the name of the parent ketone, *e g*,

$CH_3 \cdot CO \cdot CO_2H$	$CH_3 \cdot CO \cdot CH_2 \cdot CO_2H$	$CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$
α-Keto propionic acid, Acetyl-formic acid, Propanone acid	β-Keto butyric acid, Acetoacetic acid, Butane 3 one 1 acid	γ-Keto valeric acid, β Acetyl propionic acid, Pentane 4 one-1 acid

The α- and γ-keto-acids are stable even in the free state, but the free β-keto-acids readily undergo decomposition

In the protein metabolism of the living organism α-ketonic acids are formed by the oxidative deamination of α amino acids This is the commonest method by which amino-acids are decomposed in the animal body It is assumed that an α hydroxy-α-amino-acid occurs as an intermediate



Pyruvic acid, pyro racemic acid, *acetyl-formic acid*, $CH_3 \cdot CO \cdot COOH$, is the simplest α-keto-acid, and is prepared by distilling tartaric acid with potassium hydrogen sulphate (hence the name) It may be synthesised by the hydrolysis of acetyl cyanide

$$CH_3 \cdot CO \cdot Cl \xrightarrow{KCN} CH_3 \cdot CO \cdot CN \xrightarrow{H_2O} CH_3 \cdot CO \cdot COOH$$

α-Ketonic acids, in general, are prepared by hydrolysing the nitriles obtained by treating acid chlorides with potassium cyanide This method of preparation also confirms their constitution as α-keto acids

Pyruvic acid is a colourless liquid of pungent smell, miscible in all proportions with water, alcohol and ether It solidifies at low temperatures, melts again at 9°, and boils at 165° with partial decomposition It shows the reactions of a ketone in addition to those of an acid, forming an oxime and a hydrazone and combining with HCN Like other ketones it also undergoes condensation, yielding a benzene derivative (*uvitic acid*)

Methylglyoxal, *pyruvic aldehyde*, $CH_3 \cdot CO \cdot CHO$, is the simplest example of a keto aldehyde It may be obtained by hydrolysing iso nitrosoacetone with dilute sulphuric acid When heated to 100° with water, or more rapidly and completely on standing with cold dilute alkali, methylglyoxal is converted into lactic acid

A considerable amount of attention has recently been directed towards pyruvic acid and its aldehyde in connection with physiological processes In the living organism pyruvic acid may be transformed into alanine, lactic acid, acetoacetic acid or acetaldehyde, all of these changes being equilibrium reactions Pyruvic acid is thus assigned a central position in the conversion of the various constituents of the

body (proteins, carbohydrates, fats) into one another [1] (see also p 303) The rôle of the acid and its aldehyde in alcoholic fermentation has been investigated carefully by Neuberg [2] (p 139) In this connection Abderhalden states that there is no longer any doubt that compounds of three carbon atoms (pyruvic acid, lactic acid, glyceric aldehyde and pyruvic aldehyde, etc) form the common channel through which the carbohydrates, fats and proteins or amino-acids are mutually interconvertible

Aceto acetic acid, *β keto butyric acid*, CH_3 CO CH_2 COOH, is prepared from its esters by hydrolysis with cold dilute alkali It is obtained on acidification as a viscous liquid, which very readily decomposes into acetone and carbon dioxide Acetoacetic acid occurs in the urine of diabetic patients, and is an important decomposition product of fatty acids in the organism Otherwise the free acid is of little interest

Acetoacetic ester, CH_3 CO CH_2 $COOC_2H_5$, was discovered in the year 1863 by Geuther It is prepared by the condensation of ethyl acetate in the presence of sodium

Metallic sodium is added to purified ethyl acetate, when a reaction gradually sets in, as shown by the evolution of hydrogen and the boiling of the liquid After all the sodium has dissolved, the mixture contains excess of ethyl acetate together with sodium ethoxide and sodium acetoacetic ester The two latter compounds separate out as a paste Free acetoacetic ester is liberated by the addition of dilute acetic acid, and forms an oily layer above the aqueous liquid It is removed and, without previous drying, is purified by fractional distillation

The reaction depends on the formation of an intermediate compound, and as we are here dealing with the classical example of ester condensation the mechanism of the process will be discussed in more detail

The older views assumed a direct action of sodium on ethyl acetate to form an intermediate sodium acetic ester, $CHNa_2$ $COOC_2H_5$ or CH_2Na $COOC_2H_5$, as in Kolbe's equation,

$$CH_3\ COOC_2H_5 + CHNa_2\ COOC_2H_5 = CH_3\ CO\ CHNa\ COOC_2H_5 + C_2H_5ONa$$

and that given later by Baeyer —

$$CH_3\ COOC_2H_5 + CH_2Na\ COOC_2H_5 = CH_3\ CO\ CHNa\ COOC_2H_5 + C_2H_5OH$$

These theories were opposed by Claisen in 1887 on the ground that the formation of sodium acetoacetic ester is not induced primarily by the action of sodium, but by sodium ethoxide produced from alcohol contained as an impurity in the acetic ester employed, also an O-sodium derivative is more probable as an intermediate compound than a C-sodium derivative

[1] Wieland and A Wingler, *Ann*, 1924, 436, 229 [2] *Ber*, 1920, 53, 1039, 1924, 57, 1436 Also "Die Gärungsvorgänge und die Zuckerumsatz der Zelle"

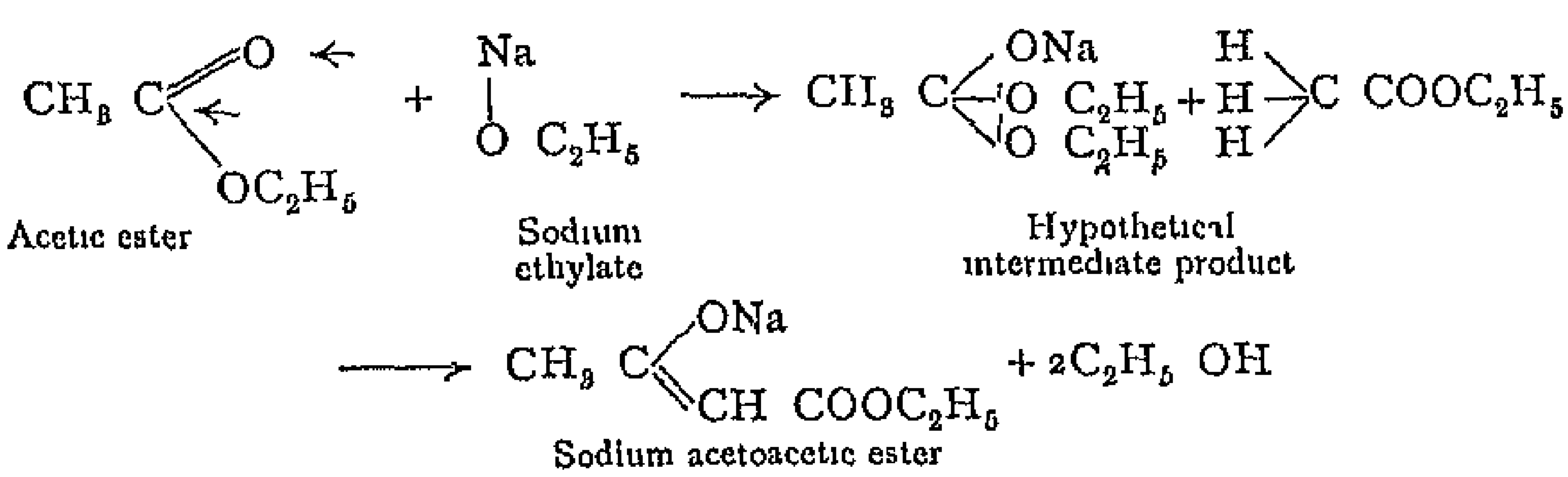
When acetic ester, free from alcohol, is placed in contact with sodium it does not react at all in the cold, and only extremely slowly on heating In the presence of a little alcohol, however, the reaction proceeds immediately If sodium is replaced by sodium ethoxide, acetoacetic ester is again formed, although less rapidly and in smaller yield Sodamide also brings about the same effect The general progress of the reaction agrees with the supposition of the preliminary conversion of sodium into sodium ethoxide Thus a very small amount of the latter may be formed from traces of alcohol already present or produced through a by reaction This ethoxide then reacts with ethyl acetate,

$$2CH_3\ COOC_2H_5 + NaOC_2H_5 = CH_3\ C(ONa)\ CH\ COOC_2H_5 + 2C_2H_5\ OH$$

liberating twice as much alcohol as was originally present, so that after the latter is converted into ethoxide the reaction proceeds to double the previous extent, and so on In actual practice the action begins slowly and gradually becomes more and more vigorous

The intermediate formation of an O sodium instead of a C sodium derivative is supported by the following considerations Claisen showed that among compounds containing the group $CO\ CH_2\ CO$, which exist in both of the forms $CO\ CH_2\ CO$ and $CO\ CH\ C(OH)$, only the latter or "acid" form gives rise to salts The other or "neutral" form yields no salts as such, but previous to salt formation isomerises into the other modification and thus gives O salts The C salts of the type $CO\ CHNa\ CO$ are therefore non existent Similar considerations have been shown to hold in the case of analogous compounds such as nitromethane, $CH_3\ NO_2$, and its homologues (see p 156) Hence it appears that in competition between the carbon of a CH_3 and the oxygen of a negative group attached to it, the metal always unites with the oxygen There is no reason to assume that acetoacetic ester is any exception to this rule The sodium salt of acetoacetic ester is therefore formulated as $CH_3\ C(ONa)\ CH\ COOH$, and since the end product is an O sodium derivative the same must hold true of the intermediate product

The two statements already quoted form the principal part of Claisen's theory relating to the acetic ester condensation In addition he has put forward suggestions as to the nature of the intermediate product and its rôle in the reaction, which are in all likelihood correct but have not yet been proved with certainty Probably the reaction takes place in the following steps —



With the aid of the above theory we can explain not only the acetoacetic ester synthesis but all important ester condensations of a similar type (see p 250)

These condensations are of great value in synthetic chemistry, and

may be further illustrated by the following examples taken from the investigations of Claisen and Wislicenus

When sodium ethoxide is allowed to interact with a mixture of two esters of monobasic acids, a ketonic ester of constitution similar to that of acetoacetic ester is formed, *e g*,

$$\underset{\text{Ethyl benzoate}}{C_6H_5\ COOC_2H_5} + \underset{\text{Ethyl acetate}}{CH_3\ COOC_2H_5} \longrightarrow \underset{\text{Benzoyl acetic ester}}{C_6H_5\ CO\ CH_2\ COOC_2H_5} + C_2H_5OH$$

If one of the reacting esters is ethyl formate, an ester of an aldehydic acid is obtained

$$\underset{\text{Formic ester}}{H\ COOC_2H_5} + \underset{\text{Acetic ester}}{CH_3\ COOC_2H_5} \longrightarrow \underset{\text{Formyl acetic ester}}{H\ CO\ CH_2\ COOC_2H_5} + C_2H_5OH$$

The use of a mixture of ethyl acetate (1 mol) and an ester of a dicarboxylic acid (1 mol) leads to the formation of keto-dicarboxylic esters

$$\underset{\text{Ethyl oxalate}}{\begin{array}{l} COOC_2H_5 \\ | \\ COOC_2H_5 \end{array}} + \underset{\text{Ethyl acetate}}{H_3C\ COOC_2H_5} \longrightarrow \underset{\text{Oxalo acetic ester}}{\begin{array}{l} CO\ CH_2\ COOC_2H_5 \\ | \\ COOC_2H_5 \end{array}} + C_2H_5OH$$

Finally, as has already been mentioned on p 250, one molecule of ester may be replaced by one molecule of a ketone, with the formation of polyketones and keto-aldehydes

$$\underset{\text{Ethyl acetate}}{CH_3\ COOC_2H_5} + \underset{\text{Acetone}}{H_3C\ CO\ CH_3} \longrightarrow \underset{\text{Acetyl acetone}}{CH_3\ CO\ CH_2\ CO\ CH_3} + C_2H_5OH$$

$$\underset{\text{Formic ester}}{H\ COOC_2H_5} + \underset{\text{Acetone}}{H_3C\ CO\ CH_3} \longrightarrow \underset{\text{Formyl acetone}}{H\ CO\ CH_2\ CO\ CH_3} + C_2H_5OH$$

Negatively-substituted β-ketonic acids may be synthesised by the action of negatively substituted aldehydes on diazo-acetic ester. In this manner *γ-trichloro-acetoacetic ester* is obtained from chloral —

$$\begin{array}{l} CCl_3 \\ | \\ CHO \end{array} + \begin{array}{l} CO\ OC_2H_5 \\ | \\ N_2CH \end{array} \longrightarrow \begin{array}{l} CCl_3 \\ | \\ CO\ CH_2\ COOC_2H_5 \end{array} + N_2$$

Acetoacetic Ester and its Synthetic Reactions

Acetoacetic ester is a colourless, pleasant-smelling liquid, b p 181°, which is sparingly soluble in water and gives a deep violet coloration with ferric chloride[1]

Owing to its great reactivity it is to be classed as one of the most important organic compounds, from which a large number of other substances may be prepared

[1] For a characteristic colour reaction of quinones with acetoacetic ester and other compounds containing a similarly attached methylene group, see W Kesting, *Ber*, 1929, 62, 1422

The utility of acetoacetic ester as a synthetic reagent depends partly on the ease with which one of the hydrogen atoms may be replaced by sodium. When allowed to interact with metallic sodium an evolution of hydrogen occurs with the simultaneous formation of a sodium salt.

$$CH_3\cdot CO\cdot CH_2\cdot COOC_2H_5 + Na \longrightarrow H + CH_3\cdot C(ONa){:}CH\cdot CO_2C_2H_5$$

The sodium salt is more conveniently prepared by treating the ester with an alcoholic solution of sodium ethoxide.

By making use of this sodium compound a variety of groups can be introduced into the acetoacetic ester molecule. On bringing it into reaction with an organic halogen compound, a separation of sodium halide takes place and the two organic radicals unite together. In the following examples the sodium derivative is written as $CH_3\cdot CO\cdot CHNa\cdot COOC_2H_5$ in order to abbreviate and simplify the equations—it should be remembered, however, that the constitution of the metallic compound is best expressed by the enolic formula.

$$CH_3\cdot CO\cdot CHNa\cdot COOC_2H_5 + I\cdot CH_3 = \underset{\text{Methyl acetoacetic ester}}{CH_3\cdot CO\cdot \underset{CH_3}{CH}\cdot COOC_2H_5} + NaI$$

$$CH_3\cdot CO\cdot CHNa\cdot COOC_2H_5 + \underset{\text{Acetyl chloride}}{Cl\cdot COCH_3} = \underset{\text{Acetyl acetoacetic ester}}{CH_3\cdot CO\cdot \underset{CH_3\cdot CO}{CH}\cdot COOC_2H_5} + NaCl$$

$$CH_3\cdot CO\cdot CHNa\cdot COOC_2H_5 + \underset{\text{Chloro acetic ester [1]}}{Cl\cdot CH_2\cdot COOC_2H_5} =$$

$$\underset{\text{Aceto-succinic ester}}{CH_3\cdot CO\cdot \underset{CH_2\cdot COOC_2H_5}{CH}\cdot COOC_2H_5} + NaCl$$

These mono-substituted esters also react with sodium ethoxide to give sodium derivatives, which by interaction with an organic halogen compound yield disubstituted acetoacetic esters, *e.g.*,

$$\underset{\text{Sodium methyl acetoacetic ester}}{CH_3\cdot CO\cdot \underset{CH_3}{CNa}\cdot COOC_2H_5} + \underset{\text{Propyl bromide}}{BrC_3H_7} = \underset{\text{Methyl propyl acetoacetic ester}}{CH_3\cdot CO\cdot \underset{CH_3\quad C_3H_7}{C}\cdot COOC_2H_5} + NaBr$$

The great synthetic value of acetoacetic ester lies less in the production of the above types of compounds than in the simpler substances to which they give rise on hydrolysis. Acetoacetic ester may be hydrolysed in two ways, which are distinguished according to

[1] In the presence of weakly dissociating solvents, addition products can be isolated from chloroacetic ester and sodium acetoacetic ester or its alkyl derivatives (Michael, *Ber.*, 1905, **38**, 3217).

the nature of the product as "**ketonic hydrolysis**" (I) and "**acid hydrolysis**" (II) respectively

$$\text{I} \quad CH_3\,CO\,CH_2\,COOC_2H_5 + HOH = \underset{\text{Acetone}}{CH_3\,CO\,CH_3} + CO_2 + C_2H_5\,OH$$

$$\text{II} \quad CH_3\,CO\,CH_2\,COOC_2H_5 + 2HOH = \underset{\text{Acetic acid}}{2CH_3\,COOH} + C_2H_5\,OH$$

Ketonic hydrolysis occurs chiefly on treatment with hot dilute acids or alkalis, or by heating with water in a closed tube to 200°, whereas acid hydrolysis is brought about by heating with concentrated alkalis Since the above-mentioned derivatives of the ester can also be hydrolysed in a similar manner to yield ketones or acids, we have here a *general method for the preparation of mono- and di-substituted methyl ketones* of the type of R CH_2 CO CH_3 and RR'CH CO CH_3, *and of mono- and di-substituted acetic acids* R CH_2 COOH and RR'CH COOH

The *electrolytic reduction* of acetoacetic ester or its substitution products leads to the formation of hydrocarbons, *e g* butane from acetoacetic ester itself

$$CH_3\,CO\,CH_2\,COOC_2H_5 \longrightarrow CH_3\,CH_2\,CH_2\,CH_3$$

Two molecules of acetoacetic ester may also be coupled up with one another (*a*) directly, by the action of iodine on sodium acetoacetic ester, (*b*) indirectly through various divalent radicals, by the condensation of acetoacetic ester with aldehydes or alkylene bromides In case (*a*) the interesting substance *diaceto-succinic ester* is formed, which has been isolated in several desmotropic modifications, and the study of which has been of considerable value in connection with the theory of tautomerism On ketonic hydrolysis it yields acetonyl-acetone (p 251)

$$\begin{array}{l} CH_3\text{—}CO\text{—}CHNa\text{—}COOC_2H_5 \\ CH_3\text{—}CO\text{—}CHNa\text{—}COOC_2H_5 \end{array} + 2I = \underset{\text{Diaceto succinic ester (keto form)}}{\begin{array}{l} CH_3\text{—}CO\text{—}CH\text{—}COOC_2H_5 \\ \qquad\qquad\quad | \\ CH_3\text{—}CO\text{—}CH\text{—}COOC_2H_5 \end{array}} + 2NaI$$

In case (*b*) acetoacetic ester derivatives are produced of the general formula

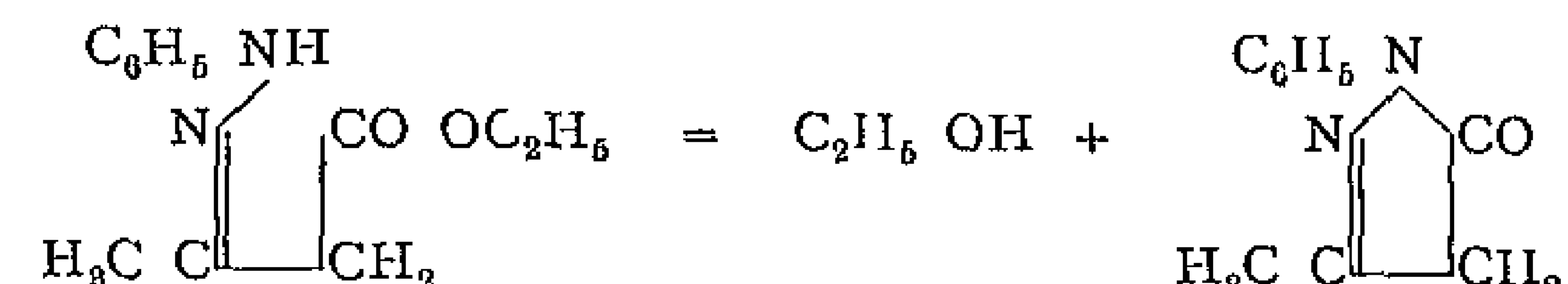
$$\begin{array}{l} CH_3\text{—}CO\text{—}CH\text{—}COOC_2H_5 \\ \qquad\qquad\quad | \\ \qquad\qquad\; CH\text{—}R \\ \qquad\qquad\quad | \\ CH_3\text{—}CO\text{—}CH\text{—}COOC_2H_5 \end{array}$$

Compounds of this type were first prepared by Hantzsch and Knoevenagel, and have also proved of interest in the development of the theory of tautomerism

Finally it should be noted that *acetoacetic ester unites with certain*

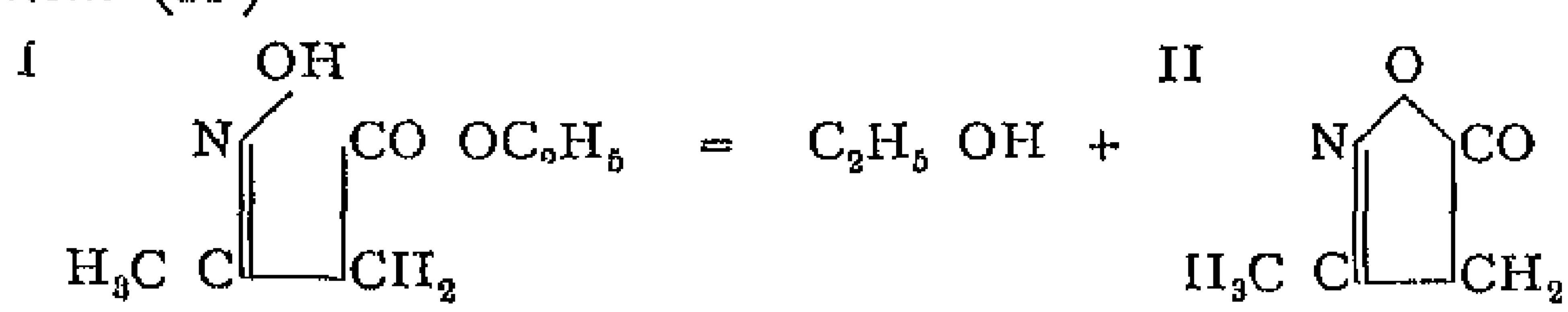
nitrogen compounds such as ammonia,[1] amines, hydrazines and hydroxylamine These reactions are of great importance for the synthesis of a variety of heterocyclic compounds, as may be seen from the following examples

With hydrazine and its monosubstitution products acetoacetic ester yields *pyrazolones* By making use of phenyl hydrazine, Knorr in 1883 succeeded in isolating the first pyrazole derivative, 1-phenyl-3-methyl-5-pyrazolone, which forms the starting point in the technical preparation of antipyrine The reaction takes place in two phases, the hydrazone of the ester being first obtained and alcohol subsequently eliminated

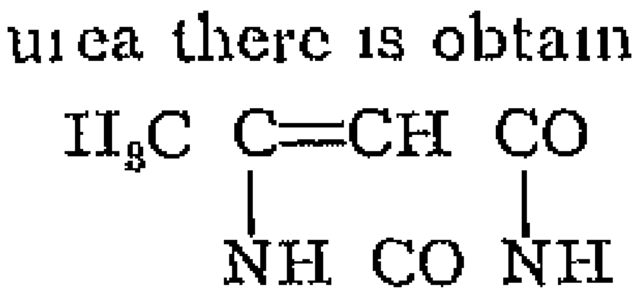


Phenyl hydrazone of acetoacetic ester — 1-Phenyl 3 methyl 5 pyrazolone

Hydroxylamine interacts with acetoacetic ester to form β-iso nitroso-butyric ester (I), which is readily transformed into *methylisoxazolone* (II)



By condensation with urea there is obtained *methyluracil*,



With nitrous acid acetoacetic ester yields *iso-nitroso-acetoacetic ester*,

$$CH_3\ CO\ C(NOH)\ COOC_2H_5$$

which easily decomposes into alcohol, carbon dioxide, and *iso-nitroso-acetone*

Tautomerism of Acetoacetic Ester

From its reactions acetoacetic ester may be classed either as the ester of a keto-acid or of an unsaturated hydroxy-crotonic acid The liquid ester is an equilibrium mixture of the keto and enol forms, the form actually in preponderance depending on various factors

I $CH_3—CO—CH_2—COOC_2H_5$ — Acetoacetic ester (β or keto form)

II $CH_3—C(OH)=CH—COOC_2H_5$ — *Aci* acetoacetic ester (α or enol form)

Acetoacetic ester represents the oldest and probably the most important example of tautomerism The problem of its constitution

[1] *Ann*, 314, 200

has now been solved, mainly owing to the knowledge gained by the investigations of Knorr [1] and his co-workers in connection with the desmotropy of diaceto-succinic ester. From these researches it was concluded that the velocity of isomerisation of the forms of acetoacetic ester should not be very high, and that a separation might be effected at low temperatures. This conclusion was confirmed by experiment.

At the temperature of a mixture of ether and solid carbon dioxide ($-78°$) it was found that the mutual interconversion of the two forms is practically arrested, and that the individual isomerides could be isolated without any great difficulty.

The Keto-form

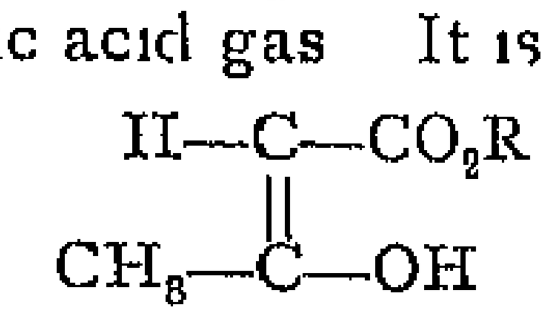
Acetyl acetic ester, $CH_3 \cdot CO \cdot CH_2 \cdot COOC_2H_5$—generally described by Knorr as the β-ester—may be obtained from the ordinary ester by freezing it out at the temperature of a mixture of ether and solid carbon dioxide. It is difficultly soluble in the majority of organic solvents at this low temperature, and crystallises out from its solutions in alcohol, ether, hexane, ligroin and other solvents which are still liquid at $-78°$. It may thus be separated by filtration. When kept cool in the above mixture, or in liquid air, the keto ester may be preserved for a very long time without noticeable change. Even at the ordinary temperature in the absence of catalysts, it only returns slowly to the equilibrium mixture during the course of weeks or months. The β-form differs comparatively little from the ordinary (equilibrium) ester, as may be seen from the following data:

	β *Ester*	*Equilibrium Mixture*
Boiling point (2 mm.)	40° to 41°	39° to 40°
Melting point	−39° (sharply)	−45° to −43° (not sharply)
Refrac. index, n_D^{10}	1.4225	1.4230 to 1.4235

While the purity of a keto-form is commonly tested by its failure to give the ferric chloride reaction, the keto-acetoacetic ester at ordinary temperatures shows the same behaviour as the equilibrium mixture, since the addition of the reagent immediately produces from both a large amount of the enolic form. On the other hand, at low temperatures, a decided difference may be observed between the behaviour of the pure keto-ester and that of the ordinary mixture.

Enolic Form

Cis hydroxy crotonic ester, $CH_3 \cdot C(OH) : CH \cdot COOC_2H_5$. This form was obtained by Knorr by treating the sodium compound of acetoacetic ester with dry hydrochloric acid gas. It is given the *cis* configuration



[1] *Ber.*, 1911, 44, 1138.

since by virtue of the neighbouring positions of the oxygen groups this should be more acidic than the *trans*-configuration,

$$\begin{array}{c} H—C—CO_2R \\ \| \\ HO—C—CH_3 \end{array}$$

and hence is probably present as such in the salts

It has been found (K H Meyer) that when acetoacetic ester is distilled in a glass flask, the alkali of which acts as a catalyst, the ester is converted into a mixture containing a higher percentage of enol form Using a quartz flask, however, the distillation occurs in the absence of catalytic influences, and it is then possible to separate the keto and enolic forms by taking advantage of the difference in boiling points, little interconversion occurring during the operation By applying the latter procedure to the richly enolic mixture obtained by distillation in an ordinary flask the enolic form of the ester is readily prepared [1]

The enolic ester is a colourless oil possessing a powerful and pleasant fruity odour It does not solidify at the temperature of the ether-carbon dioxide mixture, but in liquid air hardens to a crystalline mass In small quantities it may be distilled in a high vacuum without much change, boiling at about 33° The enolic form differs from the keto form and the equilibrium mixture, it has a much higher refractive index and rapidly gives the colour reaction with ferric chloride, even at low temperatures

Ketonisation of the Enol-ester —The enol-form can only be preserved at low temperatures At room temperature isomerisation is soon noticeable, and even the purest preparation changes back into the equilibrium mixture during the course of ten to fourteen days

The velocity of isomerisation of the desmotropic forms of aceto acetic ester may be considerably increased by catalytic influences Contact with soft alkali glass, with a little vapour of hydrochloric acid, tripropylamine or cigarette smoke, or merely handling the liquid in the impure air of a laboratory, is sufficient in a few seconds or minutes to convert the enolic form into the equilibrium mixture

The Equilibrium Mixture

Under ordinary conditions the ester is a mixture containing only about 7 per cent of the enolic form In the vaporous state it is found that the equilibrium varies with temperature and pressure between the limits of 10 and 30 per cent enol, so that according to the conditions of experiment the freshly distilled ester may possess the same or a higher enolic content than the normal equilibrium mixture If the ester is in solution in a volatile solvent, the relative proportions of the isomerides

[1] K H Meyer and co workers, *Ber*, 1920, 53, 1410, 1921, 54, 579

present may be determined by cooling to $-78°$, removing the solvent *in vacuo*, and estimating the composition of the residual mixture by measuring the refractive index A 30 per cent solution in ether is thus found to contain 11 per cent of the enol form

Laevulinic acid, *β-acetyl-propionic acid*, $CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH$, is the simplest γ-ketonic acid It is formed when a hexose, especially laevulose, is boiled with dilute sulphuric or hydrochloric acid Laevulinic acid is prepared by heating starch or cane sugar with hydrochloric acid It may be obtained synthetically by combining sodium acetoacetic ester with chloro acetic ester and submitting the resulting product to ketonic hydrolysis

$$\begin{array}{l} CH_3 \cdot CO \cdot \underset{\displaystyle COOC_2H_5}{\underset{|}{CH}} \cdot CH_2 \cdot COOC_2H_5 \longrightarrow CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \cdot COOH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad + CO_2 + 2C_2H_5OH \end{array}$$

The acid is crystalline, melts at 32 5° and boils with slight decomposition at 250° It is very readily soluble in water, alcohol, and ether, shows the characteristic reactions of ketones (formation of oxime, hydrazone, etc), and on electrolysis of its potassium salt yields 2 7-octane dione

$$\begin{array}{l} CH_3 \cdot CO \cdot CH_2 \cdot CH_2—COO—K \\ CH_3 \cdot CO \cdot CH_2 \cdot CH_2—COO—K \end{array} + 2H_2O = \begin{array}{l} CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \\ \qquad\qquad\qquad\quad | \\ CH_3 \cdot CO \cdot CH_2 \cdot CH_2 \end{array} + 2KHCO_3 + H_2$$

When heated for a considerable time at their boiling-points, γ ketonic acids lose water and pass into unsaturated lactones Like γ-diketones, they may also be used in the preparation of pyrrole derivatives

XV

Polybasic Acids

I —SATURATED DIBASIC ACIDS, $C_nH_{2n}(COOH)_2$

Formation —Dibasic acids are found to some extent in nature, and may be obtained artificially by methods similar to those used for the monobasic acids (see p 184) Chief among these are the oxidation of the corresponding glycols, aldehydes, hydroxy-acids or aldehydic acids, the hydrolysis of dicyanides, *e g* $CN \cdot CH_2 \cdot CH_2 \cdot CN$, or of cyano-substituted monocarboxylic acids, *e g* $CN \cdot CH_2 \cdot COOH$, and the acid hydrolysis of substituted acetoacetic esters (see p 260), *e g*

$$\underset{\text{Sodium acetoacetic ester}}{CH_3\ CO\ CHNa\ COOEt} \xrightarrow{Cl\ CH_2\ COOEt}$$

$$\underset{\text{Aceto-succinic ester}}{CH_3\ CO\ CH\left\langle\begin{array}{l}COOEt\\ CH_2\ COOEt\end{array}\right.} \xrightarrow[\text{hydrolysis}]{\text{Acid}} \underset{\text{Succinic acid}}{\begin{array}{l}CH_2\ COOH\\ |\\ CH_2\ COOH\end{array}}$$

Properties.—The dibasic acids are solid crystalline compounds of strong acidic character In most cases they dissolve readily in water, the solubility of an acid containing an uneven number of carbon atoms being greater than that of the next higher acid with an even number A similar regularity is found in the melting-points, an acid with an even number of carbon atoms melting higher than the following member containing an odd number [1]

A point to be noted is the varying behaviour of the dibasic acids under the influence of heat In some cases anhydrides are formed, whilst in others carbon dioxide is eliminated

Oxalic acid, HOOC COOH, and all those homologues in which, as in the case of malonic acid, $CH_2(COOH)_2$, the two carboxyl groups are attached to the same carbon atom, decompose on heating to give carbon dioxide and a monobasic acid

$$\underset{\text{Oxalic acid}}{HO_2C.CO_2H} = CO_2 + \underset{\text{Formic acid}}{H\ CO_2H}$$

$$\underset{\text{Malonic acid}}{HO_2C\ CH_2\ CO_2H} = CO_2 + \underset{\text{Acetic acid}}{CH_3\ CO_2H}$$

On the other hand, dibasic acids in which the carboxyl groups are linked to different carbon atoms—as in succinic and glutaric acids—generally lose a molecule of water under the influence of heat and yield an intramolecular anhydride, *e g*

$$\underset{\text{Succinic acid}}{\begin{array}{l}CH_2\text{—}COOH\\ |\\ CH_2\text{—}COOH\end{array}} = H_2O + \underset{\text{Succinic anhydride}}{\left.\begin{array}{l}CH_2\ CO\\ |\\ CH_2\ CO\end{array}\right\rangle O}$$

$$\underset{\text{Glutaric acid}}{CH_2\left\langle\begin{array}{l}CH_2\ COOH\\ CH_2\ COOH\end{array}\right.} = H_2O + \underset{\text{Glutaric anhydride}}{CH_2\left\langle\begin{array}{l}CH_2\ CO\\ CH_2\ CO\end{array}\right\rangle O}$$

The tendency towards anhydride formation of this character varies very largely with different acids It is particularly marked in cases where by elimination of water a five- or six-membered ring may be formed, and it must be assumed that this type of reaction depends on the relative positions in space of the two carboxyl groups

Those dicarboxylic acids in which the two acid groups are separated by more than four carbon atoms either volatilise unchanged on heating or undergo radical decomposition accompanied by charring

[1] See D A Fairweather, *Phil Mag*, 1926 [7], 1, 944

Nomenclature and Isomerism.—The majority of the acids take their names from their origin or method of preparation. According to the "Geneva nomenclature" the names are derived from those of the corresponding hydrocarbons, in the same manner as in the case of monobasic acids.

Among the higher members a number of structural isomerides are possible, according to the relative positions of the two carboxyl groups in the carbon chain.

Of the very large number of compounds belonging to this class, only the more important will be described here.

Oxalic acid, *ethane diacid*, HOOC.COOH, occurs very extensively in the vegetable kingdom, particularly as the potassium salt in plants of the *oxalis* and *rumex* families. In the animal organism it is found as the calcium salt. It is formed during the oxidation of many organic compounds, and is prepared industrially from cellulose by fusing sawdust with sodium or potassium hydroxide in iron pans at about 240°.

The sawdust, preferably obtained from a soft wood, is uniformly impregnated with the alkali, two parts of the latter being used to one part of wood. After fusing the mixture till all the cellulose has disappeared, the melt is extracted with hot water, and the sparingly soluble sodium oxalate allowed to crystallise out. By the addition of milk of lime the sodium salt is converted into calcium oxalate and sodium hydroxide, from the former of which free oxalic acid is obtained by treatment with sulphuric acid.

$$Na_2C_2O_4 + Ca(OH)_2 = CaC_2O_4 + 2NaOH; \quad CaC_2O_4 + H_2SO_4 = CaSO_4 + H_2C_2O_4$$

The sodium hydroxide contained in the mother liquors is recovered and utilised for the oxidation of further quantities of cellulose.

Additional methods of preparing oxalic acid are by the rapid heating of sodium formate,

$$2HCOONa = H_2 + C_2O_4Na_2$$

and by the direct combination of carbon dioxide with sodium at 360°:

$$2CO_2 + 2Na = Na_2C_2O_4$$

Properties.—Oxalic acid crystallises in monoclinic prisms containing 2 mols. water of crystallisation. The anhydrous acid melts at 190° and the hydrated form at 101°. Oxalic acid is poisonous. When carefully heated to 150° it sublimes, but on rapid heating it decomposes partly into carbon monoxide and formic acid (see p. 185), and partly into carbon dioxide, carbon monoxide and water. These last products are obtained exclusively on warming oxalic acid with concentrated sulphuric acid or acetic anhydride.

$$H_2C_2O_4 = CO_2 + CO + H_2O$$

The addition of very small quantities of water to the sulphuric acid results in a marked diminution in the velocity of decomposition.

When treated with potassium permanganate in acid solution, oxalic

acid is readily oxidised to carbon dioxide and water, a reaction frequently utilised in volumetric analysis

$$H_2C_2O_4 + O = 2CO_2 + H_2O$$

By the electrolytic reduction of oxalic acid in sulphuric acid solution, using a lead or mercury cathode, Tafel and Friedrichs obtained good yields of glyoxalic acid [1]

Oxalic acid and its antimony salt are used as mordants in the printing and dyeing industries It is also employed for whitening leather, removing ink and rust stains, bleaching and cleaning straw and stearine goods, in the manufacture of inks and the preparation of certain coal-tar dyes Ferrous oxalate is used as a photographic developer, and potassium ferric oxalate, $K_3Fe(C_2O_4)_3$, in platinum printing

Salts of Oxalic Acid

Only the alkali salts of oxalic acid are soluble in water In addition to the neutral and acid salts, *tetroxalates* are known, formed by the combination of a molecule of the acid salt with a molecule of oxalic acid, *e g* the *potassium tetroxalate* of commerce, $KHC_2O_4,H_2C_2O_4,2H_2O$ The *calcium salt*, CaC_2O_4,H_2O, is insoluble in water or acetic acid, and is used for the detection and quantitative estimation of both calcium and oxalic acid The oxalates of silver and mercury, on being heated, decompose explosively into the metal and carbon dioxide Among the above mentioned oxalates of iron, potassium ferric oxalate, $K_3Fe(C_2O_4)_3$, is of special interest In sunlight, an aqueous solution of this salt is rapidly reduced to potassium ferrous oxalate,

$$2K_3Fe(C_2O_4)_3 = 2K_2Fe(C_2O_4)_2 + K_2C_2O_4 + 2CO_2$$

and this property is utilised in the following manner in platinum printing The photographic negative is laid on paper which has been prepared with potassium ferric oxalate, and exposed to light Where the light penetrates, reduction takes place On now bringing the paper into a solution of platinum chloride, the ferrous oxalate present reduces the solution, depositing metallic platinum on those parts affected by the light

Esters and Other Derivatives of Oxalic Acid

Dimethyl oxalate, $CH_3OOC\ COOCH_3$, m p 51°, b p 162°, is useful in the preparation of pure methyl alcohol The solid ester obtained from the crude alcohol is readily purified by crystallisation, and may then be hydrolysed to yield oxalic acid and the pure alcohol *Diethyl oxalate*, $C_2H_5OOC\ COOC_2H_5$, b p 186°, condenses with acetic ester to give oxalo acetic ester (p 258) *Oxamic acid*,[2] $HOOC\ CONH_2$, is the mono amide of oxalic acid, and is formed by heating ammonium hydrogen oxalate It is a powder, melting with decomposition at 210° *Oxamide*, $NH_2\ OC\ CO\ NH_2$, the diamide of oxalic acid, is formed in a variety of ways, such as by the action of ammonia on ethyl oxalate It is a white powder which is almost insoluble in water

Malonic acid, $CH_2(COOH)_2$, occurs in beetroot It is obtained from chloroacetic acid by heating it with potassium cyanide to give cyanoacetic acid, and subsequent hydrolysis

$$CH_2\begin{cases}Cl\\COOH\end{cases} \longrightarrow CH_2\begin{cases}CN\\COOH\end{cases} \longrightarrow CH_2\begin{cases}COOH\\COOH\end{cases}$$

[1] *Ber*, 1904, 37, 3189 [2] The mono amides of dibasic acids are known generally as amic acids

Malonic acid crystallises in large leaves or plates, m p 132° When heated it decomposes into carbon dioxide and acetic acid

Its esters are of great value in the synthesis of organic compounds

Diethyl malonate, $CH_2(COOC_2H_5)_2$, is conveniently prepared from cyanoacetic acid by the action of alcohol and sulphuric acid, the malonic acid first produced being converted into the ester[1] It is a colourless liquid of faintly aromatic smell, and boils at 198° On treatment with phosphorus pentoxide it yields the double ketene O C C C O, known as *carbon suboxide*[2] The latter is a liquid of powerful odour boiling at 7°

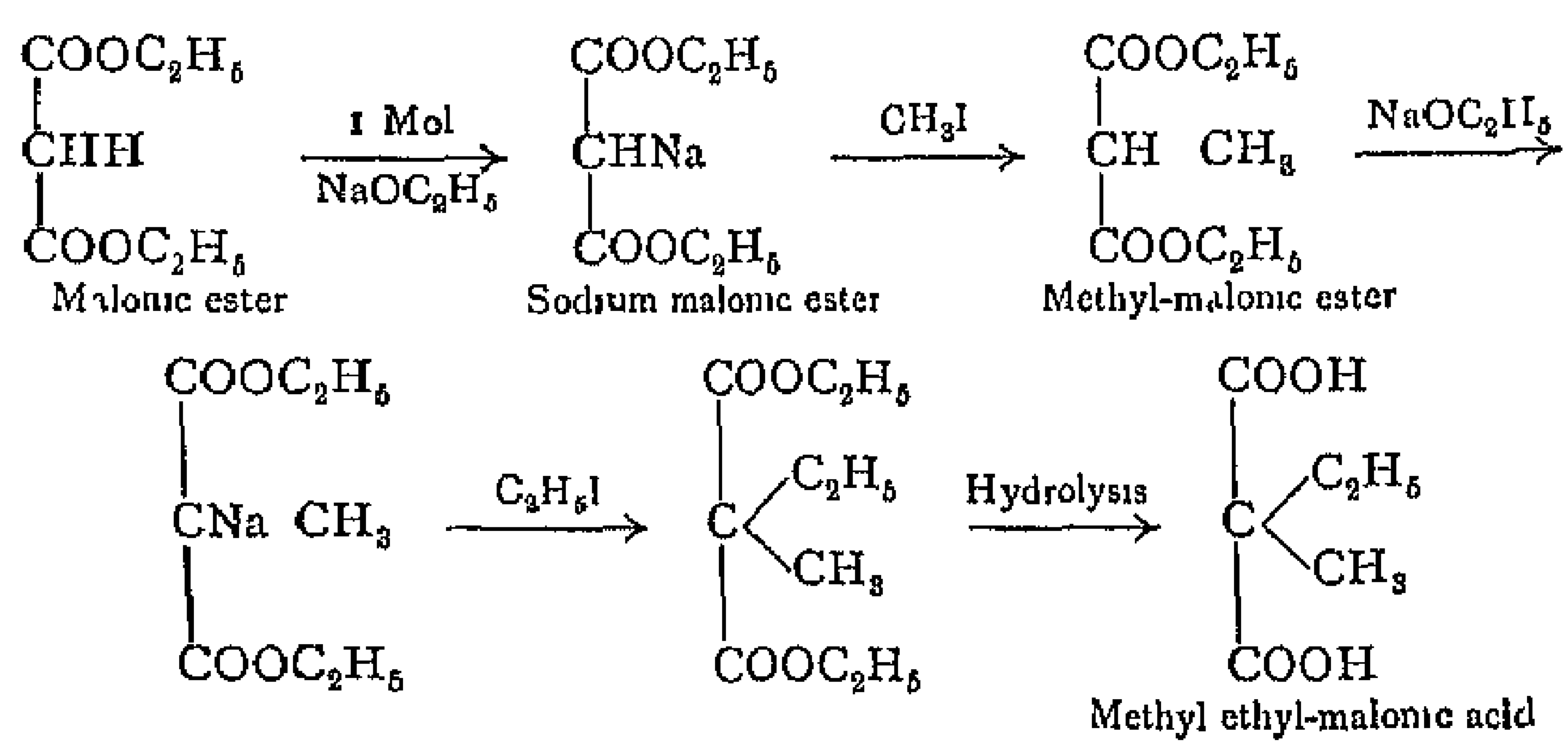
$$\underset{\text{Ethyl malonate}}{CH_2(CO_2C_2H_5)_2} = \underset{\text{Ethylene}}{2C_2H_4} + 2H_2O + \underset{\text{Carbon suboxide}}{OC\ C\ CO}$$

Malonic acid itself also decomposes into carbon suboxide on heating with phosphorus pentoxide, and is recommended by Diels as the best starting material for the preparation of this compound

Esters of malonic acid resemble acetoacetic ester in that—owing to the influence of the neighbouring carbonyl groups—the two hydrogen atoms of the methylene group may be replaced successively by sodium The metal can then be exchanged for other groups by bringing the sodium compound into reaction with organic halogen compounds (*e g* alkyl and acyl halides)

In the "malonic ester syntheses" we have a valuable method for the preparation of dibasic acids of the general types $CHX(COOH)_2$ and $CXY(COOH)_2$

The following scheme represents a typical synthesis of this kind For further information reference should be made to the similar case of acetoacetic ester, which has been dealt with in detail



It has already been mentioned that those dicarboxylic acids in which the two acid groups are separated by a single carbon atom readily lose carbon dioxide when heated, and pass into monobasic acids

[1] W A Noyes, *J Am C S*, 1896, 18, 1105 [2] Diels and Wolf, *Ber*, 1906, 39, 689, 1907, 40, 355, 1926, 59, 2555 M J Edwards and J M Williams, *J C S*, 1927, 855

From the dibasic acids synthesised by the above method, we can therefore obtain by the action of heat substituted acetic acids of the type $CH_2X \cdot COOH$ and $CH(XY) \cdot COOH$.

For example,

$$\begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>C<\!\!\begin{matrix}COOH\\COOH\end{matrix} \longrightarrow \begin{matrix}CH_3\\C_2H_5\end{matrix}\!\!>C<\!\!\begin{matrix}H\\COOH\end{matrix} + CO_2$$

Methyl ethyl malonic acid — Methyl ethyl acetic acid

These substituted acetic acids can also be obtained by the acid hydrolysis of acetoacetic ester derivatives, as described on p. 260. In this case, however, a certain amount of ketonic hydrolysis usually occurs at the same time, reducing the yield of acid. On the other hand, in malonic ester syntheses the substituted malonic acids decompose in one direction only, and it is therefore more expedient to use this method for the preparation of the homologous fatty acids.

Like acetoacetic ester, malonic ester may also react in the *enolic form*, $H_5C_2OOC \cdot CH : C(OH) \cdot OC_2H_5$, although the proportion of this present in the ordinary ester appears to be extremely small. Probably the sodium derivative is of this type.

Electrosynthesis by Means of Malonic Ester

Syntheses effected by electrolytic means in organic chemistry are not very numerous, but the method has been applied with great success to salts of the monoesters of dibasic acids, and of malonic acid in particular.

Brown and Walker[1] found that on electrolysing the aqueous solution of an alkali salt of a monoester of a dicarboxylic acid (*e.g.* potassium ethyl malonate) the free carboxyl group was eliminated as carbon dioxide, and two of the residues thus produced united together, as in the Kolbe synthesis of ethane (p. 103), to form the diester of a higher dicarboxylic acid. In this manner the more complex dibasic acids were prepared synthetically from lower homologues: *e.g.*, succinic ester was obtained from potassium ethyl malonate:

$$\underset{\text{Potassium ethyl malonate}}{2C_2H_5O \cdot OC \cdot CH_2 \cdot COOK} \longrightarrow \underset{\text{Diethyl succinate}}{C_2H_5OOC \cdot CH_2 \cdot CH_2 \cdot COOC_2H_5}$$

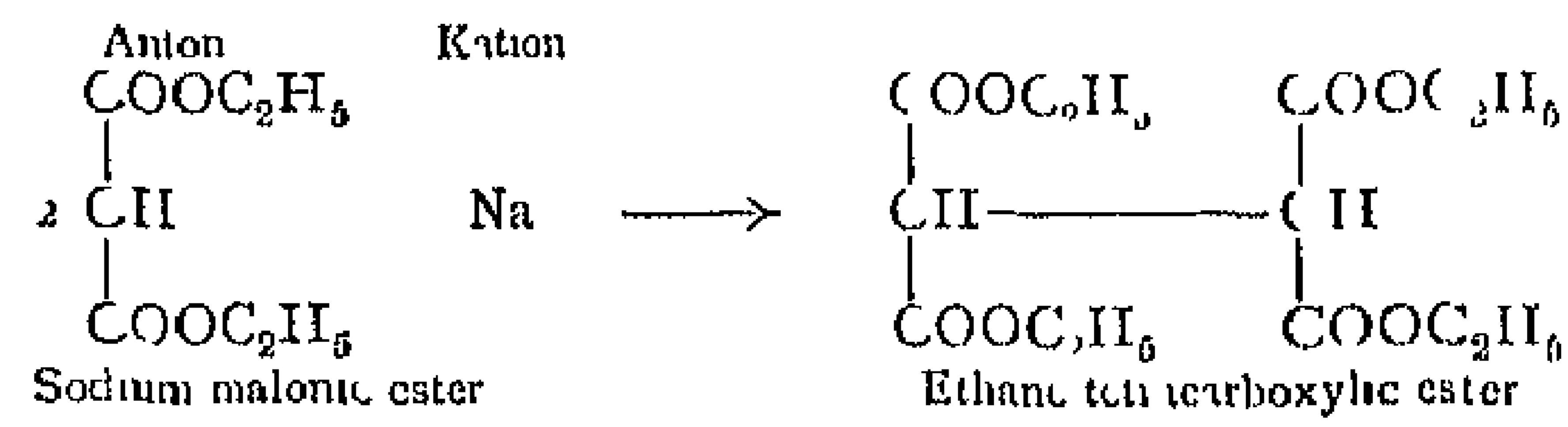
By starting from the ethyl potassium salt of a substituted malonic acid the reaction gives a substituted succinic ester, *e.g.*:

$$C_2H_5OOC \cdot CHCH_3 \cdot COOK \longrightarrow C_2H_5OOC \cdot CH(CH_3) \cdot CH(CH_3) \cdot COOC_2H_5$$

If both carboxyl groups in a dibasic acid are esterified, the diester functions as an acid on electrolysis, provided that a methylene group of pronounced acidic character is present. The dialkyl esters of sodium malonic acid, in particular, resemble carboxylic acids in their behaviour

[1] *Ann.*, 1891, 261, 107; 1893, 274, 41.

on electrolysis, the two anions uniting together to form *ethane-tetra carboxylic ester*



The compound so obtained is thus the same as that formed by removing the sodium with iodine

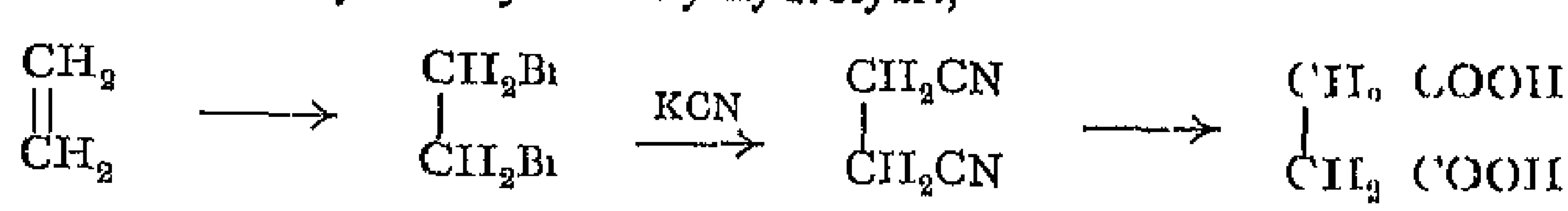
It may also be mentioned that when a salt of a monoester of a dibasic acid is mixed with a salt of a fatty acid and submitted to electrolysis, an ester of a higher monobasic acid is produced In this way ethyl butyrate is obtained from a mixture of potassium acetate and ethyl potassium succinate

$$CH_3\ COOK + KOOC\ CH_2\ CH_2\ COOC_2H_5 \longrightarrow CH_3\ CH_2\ CH_2\ COOC_2H_5$$

Methyl malonic acid, $CH_3\ CH(COOH)_2$, m p 130°, is prepared from sodio malonic ester and methyl iodide, or by the hydrolysis of cyanopropionic acid, $CH_3\ CH(CN)\ COOH$ It is isomeric with succinic acid and is therefore sometimes termed isosuccinic acid or ethylidene succinic acid At 150° it decomposes into propionic acid and CO_2

Succinic acid, *ethylene succinic acid, butane diacid*, $HOOC\ CH_2\ CH_2\ COOH$, occurs in amber, in a few resins and brown coals, in many plants and in the animal organism It is formed in small amounts during the alcoholic fermentation of sugar, and is prepared by distillation of amber or from calcium malate by fermentation It may be synthesised by the following reactions

1 From ethylene cyanide by hydrolysis,



2 From malonic acid by electrolytic methods (see p 269); also by the "malonic ester synthesis,"

$$\underset{\text{Sodium malonic ester}}{(COOC_2H_5)_2CHNa} + \underset{\text{Chloroacetic ester}}{Cl\ CH_2\ COOC_2H_5} \longrightarrow \underset{\text{Ethane tricarboxylic ester}}{(COOC_2H_5)_2CH\ CH_2\ COOC_2H_5}$$

$$\xrightarrow{\text{hydrolysis}} (COOH)_2CH\ CH_2\ COOH$$

$$\xrightarrow{\text{heat}} HOOC\ CH_2\ CH_2\ COOH + CO_2$$

It is readily seen that alkyl-substituted succinic acids can also be obtained by this reaction, by combining alkyl-substituted sodium

malonic esters, $NaRC(COOC_2H_5)_2$, with alkyl-substituted chloroacetic esters of the general formula

$$Cl\ CHR'\ COOC_2H_5 \quad \text{and} \quad ClCR'R''\ COOC_2H_5$$

An additional method of passing from the malonic acid to the succinic acid series consists in removing sodium from sodium malonic esters by means of iodine, hydrolysing the ethane tetracarboxylic ester so formed (p 270), and then splitting off carbon dioxide from the free tetracarboxylic acid at a higher temperature

Among other reactions leading to the formation of succinic acid may be mentioned the reduction of its hydroxy derivatives malic and tartaric acids, and also of fumaric and maleic acids

Succinic acid crystallises in monoclinic prisms, m p 185°, and boils at 235° with partial conversion into the anhydride At the ordinary temperature it is soluble in twenty parts of water The potassium salt yields ethylene on electrolysis

Brown and Walker (p 269) found that the main product of the electrolysis of ethyl potassium succinate was the diethyl ester of adipic acid

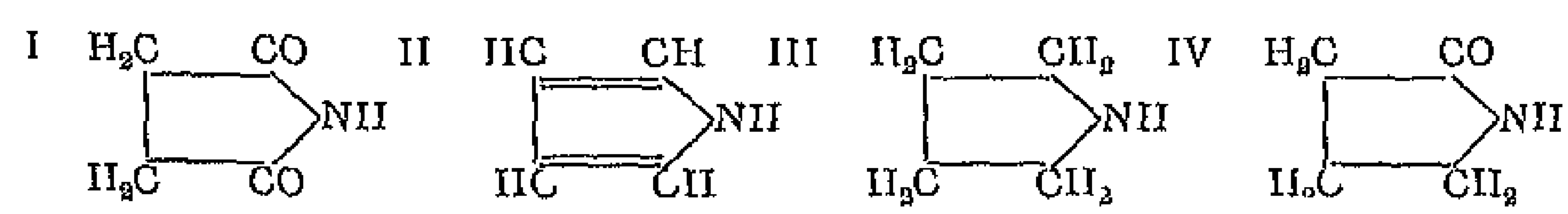
$$2COOC_2H_5\ (CH_2)_2\ COOK \longrightarrow COOC_2H_5\ (CH_2)_4\ COOC_2H_5$$

Among other important *derivatives of succinic acid*, the hydroxy compounds, **malic acid** and **tartaric acid**, and the **ester of diaceto succinic acid**, are described in detail later

Of the *succinates*, the alkali salts are readily soluble in water, and those of other metals insoluble or only sparingly soluble

Esters **Methyl succinate**, $C_2H_4(COOCH_3)_2$, is a solid at ordinary temperatures and melts at 19°, the **ethyl ester** boils at 218°, and undergoes a remarkable condensation under the influence of sodium, to give a cyclic compound *succinylo succinic ester* (p 460)

Succinimide (I) is produced by heating ammonium succinate, and is a solid m.p 126° and b p 228° It is acidic in character, the hydrogen of the NH— group being replaceable by metals When distilled with zinc dust it is converted into *pyrrole* (II), and when reduced with sodium in boiling alcoholic solution it yields *pyrrolidine* (III) Electrolytic reduction gives *pyrrolidone* (IV)



Mono and dibromo succinic acids, COOH CHBr CH_2 COOH and COOH CHBr CHBr COOH, are readily obtained by the action of bromine on succinic acid, and are used in the synthesis of the hydroxy acids.

Methyl succinic acid, pyro tartaric acid, $\begin{array}{l} CH_3\ CH\ COOH \\ \quad\ \ | \\ \quad\ CH_2\ COOH \end{array}$,

m p 112°, is formed (together with pyruvic acid) by the dry distillation of tartaric acid, also by the acetoacetic ester synthesis, etc It contains

an asymmetric carbon atom and can be resolved into its optically active components by means of strychnine

Symmetrical dialkyl succinic acids, such as dimethyl-succinic acid, COOH CH(CH_3) CH(CH_3) COOH, are known in two forms corresponding to the meso and racemic compounds Up to the present all attempts to resolve one of these into its optically active components have failed In the case of the *sym* diphenyl-succinic acids, however, the existence of this type of isomerism has been definitely established,[1] the *r*-acid being identified by its resolution into *d*- and *l*-forms

Trimethyl succinic acid, COOH CH(CH_3) C$(CH_3)_2$ COOH, is obtained in the form of its anhydride by distillation of camphoronic acid, and is therefore of importance in connection with the constitution of camphor

Glutaric acid, *pentane diacid,* COOH CH_2.CH_2 CH_2 COOH, m p 97°, may be obtained synthetically from trimethylene bromide *via* the cyanide CN CH_2 CH_2 CH_2 CN, or from *methylene dimalonic acid* (from sodio-malonic ester and methylene iodide) by loss of carbon dioxide

$$(CO_2C_2H_5)_2CHNa + I\ CH_2\ I + NaCH(CO_2C_2H_5)_2$$
$$\longrightarrow \underset{\text{Methylene dimalonic ester}}{(CO_2C_2H_5)_2CH{-}CH_2{-}CH(CO_2C_2H_5)_2}$$
$$\longrightarrow \underset{\text{Methylene dimalonic acid}}{(CO_2H)_2CH{-}CH_2{-}CH(CO_2H)_2} \longrightarrow \underset{\text{Glutaric acid}}{CO_2H\ CH_2{-}CH_2{-}CH_2\ CO_2H}$$

The main interest of the following higher dicarboxylic acids lies in the *cyclic ketones* which may be formed by heating their calcium salts

Adipic acid, COOH $(CH_2)_4$ COOH, m p 153°, was first obtained by the oxidation of fat (*adeps,* fat) by means of nitric acid, and is best prepared by oxidising cyclohexanol with alkaline potassium permanganate The calcium salt on dry distillation yields *keto-pentamethylene* or *cyclo-pentanone* (I), together with calcium carbonate

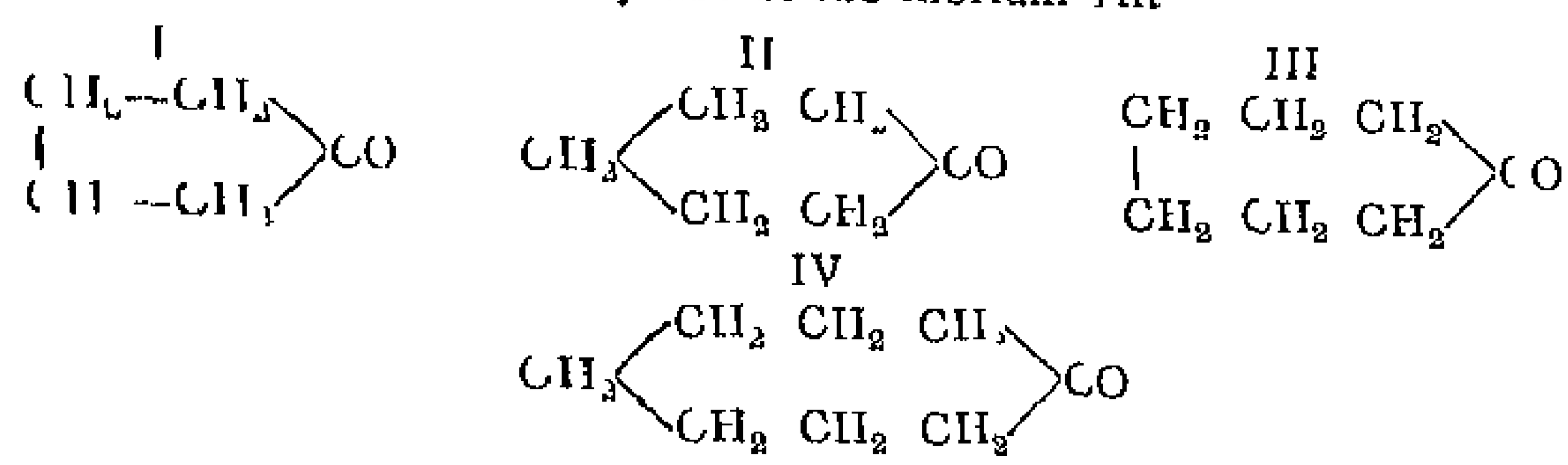
Normal pimelic acid, COOH $(CH_2)_5$ COOH, is formed synthetically from sodium malonic ester and trimethylene bromide It melts at 103°, and on distillation of the calcium salt yields *keto hexamethylene* or *cyclo hexanone* (II) It is also obtained as a degradation product of the alkaloids atropine and cocaine, thus showing that these contain the carbon chain of *n* pimelic acid in the form of a seven membered ring

Suberic acid, COOH $(CH_2)_6$ COOH, m p 140°, occurs in the skin of the toad, and is prepared by the oxidation of cork (*suber*, cork) Brown and Walker showed that the ester of this acid is formed by the electrolysis of ethyl potassium glutarate It may also be synthesised by the action of magnesium and carbon dioxide on trimethylene bromide in dry ethereal solution When the calcium salt is distilled, *keto heptamethylene, cyclo heptanone* or *suberone* (III) is obtained

Azelaic acid, COOH $(CH_2)_7$ COOH, m p 107, is formed by the oxidation of oleic acid with nitric acid, or synthetically from sodium acetoacetic ester and

[1] H Wren, *J C S*, 1915, 108, 444

pentamethylene bromide On distillation with lime it gives *cyclo octanone* (IV) but much better yields are obtained by use of the thorium salt



Sebacic acid, $COOH\ (CH_2)_8\ COOH$, m p 133, is obtained when stearic acid, spermaceti or castor oil is oxidised with nitric acid

II —UNSATURATED DIBASIC ACIDS

Those dibasic acids in which ethylene linkages are present may be regarded as dicarboxylic derivatives of the olefines, a classification which is in agreement with their chemical behaviour As acids they form derivatives similar to those of the saturated dibasic acids described above, and as olefines they possess additive properties, uniting with two atoms of hydrogen or halogen, or with one molecule of hydrogen halide The most important representatives in this group are fumaric and maleic acids, $C_4H_4O_4$, both of which have been shown to be symmetrical dicarboxylic derivations of ethylene These two acids form one of the best known and most completely investigated cases of geometrical isomerism among symmetrically substituted ethylene derivatives This type of isomerism has already been discussed in the theoretical section of this book (see p 49), to which reference should be made

Fumaric acid, *trans-butene diacid*, $\begin{array}{l} H-C-COOH \\ \quad\ \ \| \\ HOOC-C-H \end{array}$, occurs in many plants, such as Iceland moss and *Fumaria officinalis* It is formed as the chief product of reaction when malic acid is heated for a considerable time at 140° to 150°,

$$\underset{\text{Malic acid}}{COOH\ \underset{OH}{CH}-\underset{H}{CH}.COOH} = \underset{\text{Fumaric acid}}{COOH\ CH\ CH\ COOH} + H_2O$$

and also when hydrogen halide is removed from monochloro- or monobromo-succinic acid by boiling in aqueous solution Synthetically it may be obtained by the condensation of glyoxalic acid and malonic acid in the presence of pyridine

$$HOOC\ CHO + H_2C(COOH)_2 = HOOC\ CH\ CH\ COOH + CO_2 + H_2O$$

It has been shown by F Ehrlich that a widely distributed fungus, *Rhizopus nigricans* (*Mucor stolonifer*), which is a well-known cause of rotting in fruit, is capable under suitable conditions of converting considerable quantities of invert sugar into fumaric acid The

formation of the acid is greatly influenced by the nature of the nitrogen-free organic nutriment with which the fungus is supplied.

Fumaric acid is sparingly soluble in cold water, from which it crystallises in small white needles. Under ordinary pressure it possesses no melting-point, but sublimes at 200°. At a higher temperature it partially decomposes into maleic anhydride and water. On catalytic hydrogenation it is transformed into succinic acid. *Chloro-iodo-fumaric acid* may be prepared by the addition of iodine chloride to acetylene dicarboxylic acid.

Maleic acid, *cis-butene diacid,* $\begin{array}{l} H \cdot C \cdot COOH \\ \;\;\; \| \\ H \cdot C \cdot COOH \end{array}$, is not found in nature. The anhydride is the chief product of reaction when malic acid is rapidly heated to a high temperature, and is readily converted into the acid by treatment with water. Maleic acid is also obtained from fumaric acid by various methods (see below).

It is easily soluble in cold water, crystallising in large plates or prisms, m.p. 130°, b.p. 160°. At the latter temperature it breaks up into the anhydride and water.

A comparison of the dissociation constants of fumaric acid ($K = 0.093$) and maleic acid ($K = 1.17$) shows the latter to be considerably the stronger acid.

Interconversion of Fumaric and Maleic Acids

It is a characteristic of geometrical isomerides that under certain conditions they are readily transformed into one another.

Thus fumaric acid is converted into maleic anhydride on being heated, or by the action of phosphorus pentachloride, phosphorus oxychloride or phosphorus pentoxide.

Maleic acid, on the other hand, passes without difficulty into fumaric acid if heated alone at 140°, in aqueous solution at 200° to 220°, or in benzene solution at 130°. The same change may also be effected under the influence of bromine (in sunlight), or of hydrogen halides, sulphurous acid, nitrous acid or hydrogen sulphide. A trace of piperidine converts methyl maleate in a few seconds into a crystalline mass of methyl fumarate.[1]

Various theories have been put forward in explanation of these interconversions, for which reference must be made to other sources of information.

Determination of the Configuration of Geometrical Isomers in the Ethylene Series

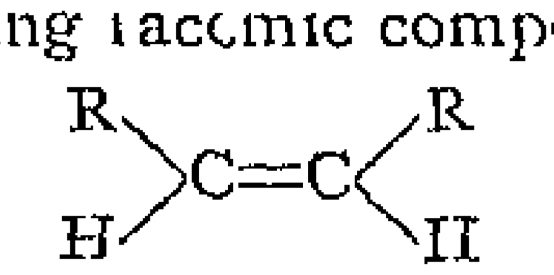
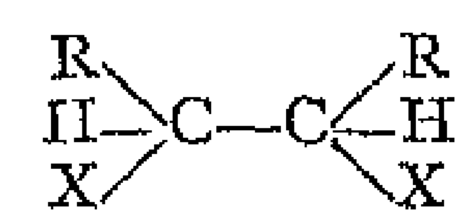
The ease with which maleic acid forms an anhydride, coupled with the fact that fumaric acid yields none, is sufficient to characterise the former without doubt as the *cis* modification, since in this case the

[1] Clemo and Graham, *J. C. S.*, 1930, 213.

carboxyl groups are in the neighbouring position necessary for anhydride formation In this property we have a general means of determining the configuration of unsaturated dibasic acids of the type COOH CR=CR COOH As maleic acid is the simplest *cis*-acid, compounds of similar configuration are sometimes known as "maleinoid forms," and those corresponding to fumaric acid as "fumaroid forms"

Among numerous examples of this kind may be mentioned the next higher homologues of fumaric and maleic acid, both of the structural formula COOH $C(CH_3)=CH$ COOH Of these, the maleinoid form is called *citraconic acid* and the fumaroid form *mesaconic acid*

Another but less certain method of determining the configuration is to convert the isomerides into symmetrical derivatives of ethane, containing two asymmetric carbon atoms The addition of two similar atoms or groups (X) to the *cis*-form of a symmetrically constituted ethylene compound (I) would be expected to lead to the formation of an inactive, internally-compensated (meso-)compound (II) On the other hand, the *trans*-form would be expected to give the corresponding racemic compound

I  II 

On treatment with potassium permanganate, for example, maleic acid takes up two hydroxyl groups to form meso-tartaric acid, whereas fumaric acid is oxidised to racemic acid

This method, however, must be applied with caution. It has been shown by McKenzie that the dibromo-succinic acid formed by addition of bromine to maleic acid is the racemic compound,[1] and not the meso-compound

An interesting unsaturated dicarboxylic acid is **glutaconic acid**, HOOC CH CH CH_2 COOH Owing to the mobility of the hydrogen attached to the carbon chain, alkyl derivatives of this acid exhibit a special type of isomerism This subject has been extensively studied by Thorpe and his co-workers For further details see p 66

Dibasic acids are also known containing triple bonds in the molecule The simplest of these is **acetylene dicarboxylic acid**, COOH C≡C COOH, which crystallises with two molecules of water, and is prepared from dibromo succinic acid by treatment with alcoholic potash When the potassium hydrogen salt of this acid is warmed with water it decomposes into carbon dioxide and potassium propiolate, CH C COOK (see p 197) The cuprous compound of potassium propiolate is oxidised by potassium ferricyanide to give copper oxide, two propiolic residues uniting to form the potassium salt of **diacetylene dicarboxylic acid**

$$2KOOC\ C\ C\ Cu + 2O = KOOC\ C\ C\ C\ C\ COOK + 2CuO$$

By a repetition of the above process **tetra acetylene dicarboxylic acid** is obtained,

$$2KOOC\ C.C\ C\ C\ Cu \longrightarrow KOOC\ C\ C\ C\ C\ C\ C\ C\ C\ COOK$$

These compounds are very unstable, and as the chain increases in length show an increasing tendency to explode

[1] *J C S*, 1912, **101**, 1196

It is to be noted that the acetylene carboxylic acids are comparatively strong acids, as may be seen from their dissociation constants. A triple bond, and to a less extent a double bond, therefore leads to an increase of acidic character.

III.—ACIDS OF HIGHER BASICITY

With regard to the constitution of acids of higher basicity, it is to be remembered that, as in the case of certain other poly-substituted compounds already discussed, the presence of more than one carboxyl group attached to the same carbon atom leads to instability. No compound is known containing more than two carboxyl groups in this state of combination.

Tricarballylic acid, *sym. propane tricarboxylic acid*,

$$CH_2(CO_2H)\cdot CH(CO_2H)\cdot CH_2(CO_2H)$$

occurs in unripe beetroots. It may be formed synthetically by various reactions, *e.g.*, from allyl tribromide, by conversion into the tricyanide and subsequent hydrolysis,

$$\underset{\text{Allyl tribromide}}{CH_2Br—CHBr—CH_2Br} \longrightarrow \underset{\text{Allyl tricyanide}}{CH_2(CN)—CH(CN)—CH_2(CN)}$$

$$\longrightarrow CH_2(CO_2H)—CH(CO_2H)—CH_2(CO_2H)$$

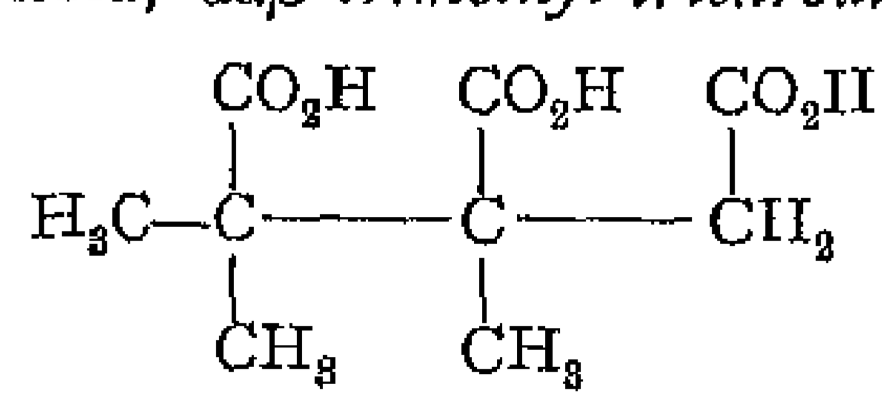
also by the condensation of sodium malonic ester and monochlorosuccinic ester. The ester so formed,

$$(C_2H_5OOC)_2CH\cdot CH(COOC_2H_5)\cdot CH_2\cdot COOC_2H_5$$

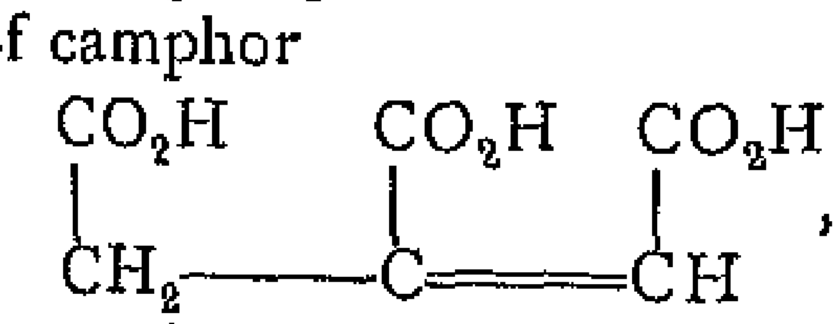
is hydrolysed and the acid heated to drive off carbon dioxide. Tricarballylic acid melts at 162° to 164° and is readily soluble in water.

A monohydroxy derivative of this acid is citric acid, which is dealt with later.

Camphoronic acid, *αaβ-trimethyl-tricarballylic acid*, m.p. 135°, is



formed by the oxidation of camphor. The determination of its constitution by Perkin and Thorpe[1] provided valuable evidence in connection with the structure of camphor.

Aconitic acid,  , is an example of an unsaturated tribasic acid. It occurs in various plants, *e.g.* in *Aconitum napellus*, in beetroot and in sugar cane, and is formed by removing the

[1] *J. C. S.*, 1897, 1169.

elements of water from citric acid On reduction it takes up two atoms of hydrogen and is converted into tricarballylic acid

Acids of higher basicity than these do not appear to occur in nature, but can be synthesised from acetoacetic ester or malonic ester In this way acids have been obtained, having as many as fourteen carboxyl groups in the molecule

XVI

Polybasic Acids containing Hydroxy, Amino, Aldehydic and Ketonic Groups

In chemical behaviour and general methods of preparation these compounds resemble the corresponding derivatives of the monobasic acids previously described

Dibasic Hydroxy Acids

The simplest compounds of this class are derived from malonic acid

Tartronic acid *hydroxy malonic acid*, COOH CHOH COOH, is formed from chloro or bromo malonic acid by replacing halogen with hydroxyl, or from glycerol by oxidation with permanganate It crystallises in large, colourless prisms which melt with evolution of carbon dioxide at 184 As will be seen later, *mesoxalic acid* may be regarded as *dihydroxy malonic acid*

Of far greater importance than the hydroxy derivatives of malonic acid are those of succinic acid, namely malic and tartaric acids

Malic acid, *hydroxy-succinic acid*, *butanol diacid*,

$$\begin{array}{l} HO\ CH\ COOH \\ \quad | \\ CH_2\ COOH, \end{array}$$

is widely distributed in the vegetable kingdom, occurring for example in sour apples, grapes and the berries of the mountain ash It is best obtained from the latter source As may be seen from the above formula it contains an asymmetric carbon atom, and may therefore exist in *d*-, *l*- and *r*-forms (see p 32) The acid obtained from the above natural sources is the *laevorotatory* form, which is frequently described as *ordinary malic acid*

r-*Malic acid* may be obtained in various ways, such as by reducing racemic acid with hydriodic acid, and by heating fumaric or maleic acid to 100° with aqueous sodium hydroxide

d-*Malic acid* is obtained by resolving the racemic form by means of the cinchonine salt, or by reducing ordinary (dextro-)tartaric acid with hydriodic acid As will be seen below, the two active malic acids can be converted into one another through the chloro-succinic acids (Walden inversion)

Ordinary *l*-malic acid forms deliquescent needles, readily soluble in

water and alcohol, but difficultly soluble in ether It melts at 100°, and on further heating yields, according to conditions, either fumaric acid or maleic anhydride On reduction it is converted into succinic acid When heated with strong sulphuric acid it yields *coumalinic acid*, with sulphuric acid and phenols it gives *coumarins* (see index)

Three of the four groups linked to the asymmetric carbon atom in malic acid are readily attacked by chemical reagents Many derivatives are therefore known which may also exhibit optical activity, provided that the asymmetry of the molecule has not been destroyed at any time during their formation The rotation of the derivative is usually in the same direction as that of the original acid, but in some cases the sign of rotation is reversed, and in others a racemic compound is formed

A peculiar phenomenon was discovered by P Walden during the interconversion of malic acids and chloro succinic acids The observed changes in optical activity may be summarised as follows —

$$\begin{tikzcd}
l\text{-Chloro succinic acid} \arrow[d, "\text{AgOH}"] \arrow[r, shift right, "\text{KOH, NH}_4\text{OH}"'] & d\text{-Malic acid} \arrow[l, shift right, "\text{PCl}_5"'] \\
l\text{-Malic acid} \arrow[r, shift left, "\text{PCl}_5"] & d\text{-Chloro succinic acid} \arrow[u, "\text{AgOH}"'] \arrow[l, shift left, "\text{KOH, NH}_4\text{OH}"]
\end{tikzcd}$$

The two changes represented by the conversion of *l* chlorosuccinic acid into *l*-malic acid on the one hand and into *d*-malic acid on the other (by use of AgOH and KOH respectively) cannot both be considered as normal reactions If one of them is a simple replacement of Cl by OH, the other must be a replacement accompanied by molecular rearrangement resulting in the production of the mirror-image of the expected structure A change of the latter type, which makes it possible to pass from one optical isomeride to the other, is termed an *optical inversion* or *Walden inversion*, and usually occurs with some degree of racemisation Many other such reactions have been studied,[1] but the cause of the inversion still awaits explanation[2]

Tartaric acids, *dihydroxy-succinic acids*, *hydroxy malic acids*, *butane diol diacids*

$$\begin{array}{ccc} & \text{H} & \\ \text{HO} & \text{C} & \text{COOH} \\ & | & \\ \text{HO} & \text{C} & \text{COOH} \\ & \text{H} & \end{array}$$

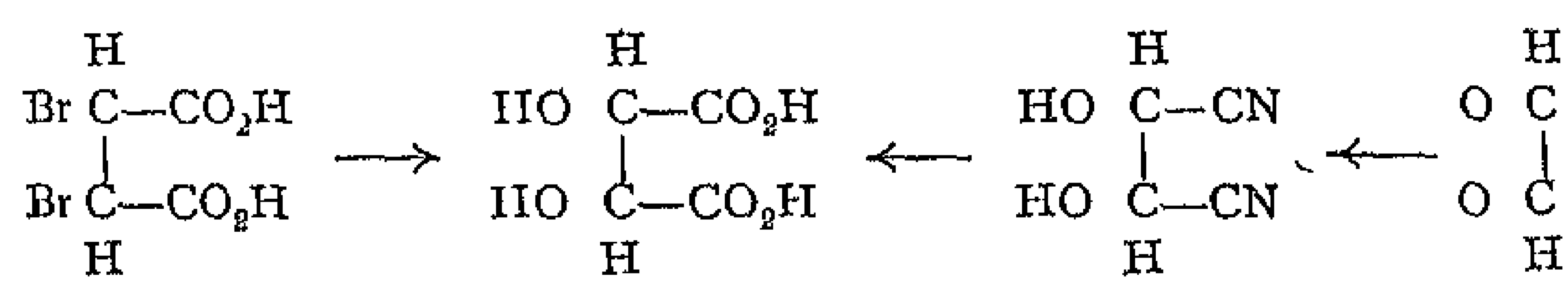
Special interest attaches to the tartaric acids, because the investigation of these compounds by Pasteur led to the first real advances in

[1] See *Optische Umkehrerscheinungen* (*Waldensche Umkehrung*) published by Vieweg and Son, Brunswick, 1920, also Cohen, *Organic Chemistry*, Vol II (Arnold) [2] A suggestion based on the polarity of the reacting complexes has been advanced by Kenyon and Phillips, *Trans Farad Soc.*, 1930, 451

our knowledge of optical activity Even to-day these acids are the best known and most completely investigated examples of compounds containing two similar asymmetric carbon atoms

As explained in the introductory section of this book (p 36), there are in agreement with theory four stereo-isomeric tartaric acids, distinguished as dextro-tartaric acid, laevo-tartaric acid, racemic acid and meso-tartaric acid respectively The following description deals in the main with their chemical properties, and for a discussion of their stereo-chemical differences reference should be made to the general section

The structural formula quoted above has been verified experimentally by the synthesis of the inactive acids, *eg* from the silver salt of dibromo succinic acid by boiling with water, or from glyoxal by addition of hydrogen cyanide and hydrolysis of the resulting nitrile



1 **Dextro-tartaric acid, *d* tartaric acid,** is the common form of tartaric acid It is found in different varieties of fruit, particularly in grapes, as the potassium hydrogen salt, $KHC_4H_4O_6$ The crude salt, known as *argol* or *tartar*, is an important by-product of the wine industry Owing to its insolubility in dilute alcohol, it separates during fermentation in hard brown crusts in the vats and storage tubs It serves as the raw material for the *technical preparation of tartaric acid*, the process being carried through in the following manner

Crude tartar is neutralised by boiling with water and chalk, when half of the original tartrate is converted into the sparingly soluble calcium salt, the other half remaining in solution as the di potassium salt

$$2KHC_4H_4O_6 + CaCO_3 = CaC_4H_4O_6 + K_2C_4H_4O_6 + CO_2 + H_2O$$

By the addition of calcium chloride, the dissolved salt is also transformed into the calcium salt The precipitated calcium tartrate is then separated and decomposed with dilute sulphuric acid The solution is filtered off from calcium sulphate and evaporated under reduced pressure in a vessel lined with lead, when crude tartaric acid crystallises out It is purified by decolorisation with animal charcoal and recrystallisation

d-Tartaric acid crystallises in monoclinic prisms, it is readily soluble in water and alcohol but insoluble in ether The solution in water is dextro-rotatory When rapidly heated the acid melts at 167° to 170° Heated with a little water to 175°, it gives a mixture containing much racemic and a little meso-tartaric acid, at 165°, on the other hand, these proportions are reversed

Inactivation of this kind is frequently met with among optically active compounds The partial or complete conversion of optically active substances into inactive mixtures of the same constitution is known as *racemisation*, and may be effected with varying degrees of ease under the influence of heat, acids, alkalis or other reagents (see p 37) In a few cases the change proceeds of itself in the apparently pure compound, the optical activity being completely lost in the course of time, the phenomenon is then termed *auto-racemisation*[1]

On being heated above its melting-point, *d*-tartaric acid parts with water and is transformed into anhydrides, which differ with the degree and duration of heating At higher temperatures the mass becomes brown and develops a smell of caramel, finally, charring sets in with the formation of a large number of decomposition products, including pyruvic and pyro-tartaric acids (pp 255, 271) When heated with hydriodic acid reduction takes place, first to malic acid and finally to succinic acid The reduction to succinic acid may also be effected under the influence of certain bacteria

Tartaric acid, cream of tartar and tartar emetic are used as mordants in dyeing and printing The acid is also employed in the preparation of effervescing drinks, baking powder and in the manufacture of artificial wine

Salts of tartaric acid, tartrates The uses of *potassium hydrogen tartrate* (*cream of tartar*) have already been mentioned On account of its comparative insolubility the formation of this compound serves as a laboratory test for potassium and tartaric acid *Sodium potassium tartrate, Rochelle salt*, $KNaC_4H_4O_6+4H_2O$, is prepared from cream of tartar and sodium carbonate It forms clear crystals, readily soluble in water *Potassium antimonyl tartrate, tartar emetic*,

$$2[KOOC \cdot CHOH \cdot CHOH \cdot COO(SbO)] + H_2O$$

is obtained by boiling cream of tartar with antimony oxide It is fairly easily soluble in water and acts as an emetic *Fehling's solution*, containing copper sulphate, Rochelle salt and caustic soda,[2] is a useful reagent When the deep blue solution is warmed with compounds possessing reducing properties, a yellowish red precipitate of cuprous oxide is formed

2. **Laevo-tartaric acid**, l-*tartaric acid*, is obtained by the resolution of racemic acid (see p 41) In its chemical and nearly all its physical properties the *l*-acid is identical with the *d*-acid It differs in rotating the plane of polarisation to the left, to the same degree as *d*-tartaric acid rotates it to the right[3] The salts of the two acids are very similar and generally isomorphous, but show opposed hemihedral facets Salts with optically active bases, however, differ also in solubility

3 **Racemic acid**, *para or* dl-*tartaric acid*, sometimes occurs with the *d*-acid in grape juice and can be isolated from the argol mother-

[1] See Walden, *Ber*, 1898, 31, 1416 [2] The presence of tartaric acids prevents the precipitation of many metals by caustic soda [3] Isomeric *d* and *l* modifications often differ in their physiological action *l* Tartaric acid, for example, is much more poisonous than the *d*-acid

liquors. Its synthesis has already been mentioned, also its formation by oxidation of fumaric acid. It is composed of equimolecular proportions of *d*- and *l*-tartaric acids, and may be obtained by mixing solutions of these two compounds.[1] The crystalline acid has the composition $2C_4H_6O_6+2H_2O$. Methods of resolving the racemic compound into the active components have already been described on p. 41.

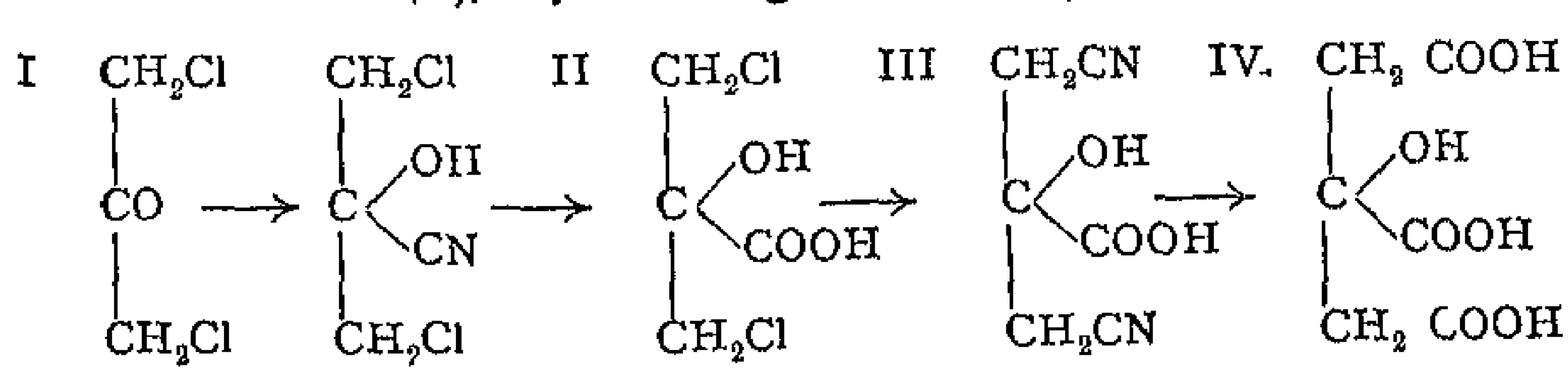
Racemic acid differs from the *d*- and *l*-acids in its optical inactivity and in forming rhombic prisms. It is less soluble than the active acids. On heating to 110°, water of crystallisation is expelled, and the anhydrous substance finally melts with effervescence at 205° to 206°. The salts, known as racemates, resemble those of tartaric acid but show no hemihedral facets. Potassium hydrogen racemate is more readily soluble than the corresponding active tartrate, and calcium racemate is more sparingly soluble than the calcium salts of the three other tartaric acids.

4. **Meso-tartaric acid**, $C_4H_6O_6+H_2O$, is formed by oxidation of maleic acid and by heating *d*-tartaric acid with water. It resembles racemic acid in being optically inactive, but unlike this compound cannot be resolved into active components. Meso-tartaric acid is therefore said to be *internally compensated* and racemic acid to be *externally compensated*. The anhydrous acid melts at 143°, considerably below the figure for racemic acid. Potassium hydrogen meso-tartrate is readily soluble in water.

Tribasic Hydroxy Acids

Citric acid, *hydroxy-tricarballylic acid*, $COOH\cdot CH_2\cdot C(OH)(COOH)\cdot CH_2\cdot COOH+H_2O$, occurs in the free state in lemons, oranges, currants and other fruit. It is prepared on the large scale (*a*) from the juice of lemons, which contains about 6 to 7 per cent of citric acid, by precipitation with milk of lime and decomposition of the calcium salt with sulphuric acid; (*b*) by fermenting sugars (*e.g.*, cane sugar, glucose, maltose) with the aid of *Citromyces pfefferianus* and *Citromyces glaber*.

Synthetically, citric acid may be obtained from symmetrical dichloro-acetone (I.), by treating it with hydrogen cyanide and



[1] From cryoscopic measurements it appears that racemic acid in solution is decomposed into its components. The experiments of Cotton, however, indicate that copper racemate exists as such in solution (see p. 34).

hydrochloric acid to give dichloro-acetonic acid (II), and converting this by means of potassium cyanide into dicyano-acetonic acid (III), which by hydrolysis yields citric acid (IV) (p 281)

It crystallises in large rhombic prisms, dissolves readily in water and alcohol, but only with difficulty in ether On heating it becomes anhydrous at 130° and melts at 153° Above this temperature citric acid parts with water to form *aconitic acid* (see p 276) If warmed carefully with concentrated sulphuric acid it decomposes into carbon monoxide, water and *acetone dicarboxylic acid*, $COOH \cdot CH_2 \cdot CO \cdot CH_2 \cdot COOH$

Citric acid is employed as a mordant in dyeing, and is used in the manufacture of lemonade

Other polybasic hydroxy acids, such as *saccharic acids*, *mannosaccharic acids*, *mucic acid* and others, will be discussed under sugars

Polybasic Amino Acids

Certain representatives of this class are of interest owing to their occurrence among the hydrolytic products of proteins

Aspartic acid, *amino-succinic acid*,
$$\begin{array}{ccc} & H & \\ H_2N & C & CO_2H \\ & | & \\ H & C & CO_2H \\ & H & \end{array},$$
contains an asymmetric carbon atom and exists in three modifications, of which *l-aspartic* acid is the most important It is found in beet molasses, and is formed as a hydrolysis product by the action of various reagents on animal and vegetable proteins When treated with nitrous acid it is converted into *l*-malic acid, the amino group being replaced by a hydroxy group By means of the Grignard reaction aspartic esters may be converted into amino glycols

Asparagine, the monoamide of amino-succinic acid,
$$\begin{array}{ccc} & H & \\ H_2N & C & CO_2H \\ & | & \\ H & C & CONH_2 \\ & H & \end{array}$$
occurs usually as the laevo variety in a number of plants, particularly in the embryo It is found in asparagus, beetroot, and in large amount in the seeds of germinating lupins The dextro-form is also present in the latter source The optically active asparagines crystallise in clear rhombic crystals, showing hemihedral facets, they differ in taste, *d*-asparagine being sweet, while the *l*-compound is decidedly insipid

On boiling with acids the amido group is hydrolysed and aspartic acid formed

Glutamic acid, *a amino-glutaric acid*, $CH_2\left\langle\begin{array}{l}CH(NH_2)\ COOH\\ CH_2\ COOH\end{array}\right.$, is formed together with aspartic acid by the hydrolysis of proteins with boiling dilute sulphuric acid, *e g*, it constitutes about 30 per cent of the crystalline products obtained from casein The highest content (*ca* 40 per cent) of glutamic acid is given by certain plant proteins, the *prolamines*, occurring in grain Glutamic acid is isolated by means of its very sparingly soluble hydrochloride The acid and many of its salts are easily converted (*e g* even on heating to 185°) into pyrrolidone carboxylic acid, and are thus closely related to the cyclic amino-acid *proline* (p 579)

Glutamine, the monoamide of glutamic acid, $C_3H_5(NH_2)(CONH_2)(COOH)$, is the nearest homologue of asparagine In the inactive form it is found associated with the latter in beetroot, the embryo of the pumpkin, and other plants

Hydroxy - glutamic acid, α - amino - β - hydroxy glutaric acid, COOH CH(NH_2) CHOH CH_2 COOH, has recently been isolated from the hydrolysis products of proteins by Dakin,[1] by his method of extraction with butyl alcohol It is crystalline, dissolves very readily in water, and on reduction with hydriodic acid yields glutamic acid With phenols and concentrated sulphuric acid it gives various colour reactions

Dibasic Aldehydic and Ketonic Acids

Mesoxalic acid, $CO(COOH)_2 + H_2O$ or $C(OH)_2(COOH)_2$, is derived from malonic acid, and its constitution presents a problem similar to that of glyoxalic acid (p 253) The compound cannot be obtained without the molecule of water quoted in the above formulæ, and it must therefore be assumed that this does not occur merely as water of crystallisation, but is united to the keto-group to form two hydroxyl groups Nevertheless, the ketonic nature of the compound is clearly shown in its power of combining with alkali bisulphite, phenyl hydrazine and hydroxylamine, and also in its behaviour on reduction Nascent hydrogen, for example, converts it into *tartronic acid*, $CHOH(COOH)_2$, containing a secondary alcoholic grouping When boiled in aqueous solution, mesoxalic acid evolves carbon dioxide and yields glyoxalic acid, a reaction which is most readily explained by the hydroxy acid formula

$$COOH\ C(OH)_2\ COOH = H\ C(OH)_2\ COOH + CO_2$$

The ethyl ester of mesoxalic acid is actually known to exist in the two forms, $C(OH)_2(COOC_2H_5)_2$ and $CO(COOC_2H_5)_2$

Mesoxalic acid is most conveniently prepared by heating dibromo-

[1] Dakin, *Biochem J*, 1918, **12**, 290

malonic acid with sodium hydroxide It crystallises in deliquescent prisms, m p 121°

Oxalo acetic ester is produced by the condensation of oxalic and acetic esters; for the mechanism of this reaction, see p 256 *et seq*

$$\underset{\text{Oxalic ester}}{C_2H_5OOC\ COOC_2H_5} + \underset{\text{Acetic ester}}{H_3C\ COOC_2H_5} \longrightarrow \underset{\text{Oxalo acetic ester}}{C_2H_5OOC\ CO\ CH_2\ COOC_2H_5}$$

The ester is a colourless oil which, like acetoacetic ester, may be regarded as a mixture of two tautomeric forms, viz,

$$C_2H_5OOC\ CO\ CH_2\ COOC_2H_5 \text{ and } C_2H_5OOC\ C(OH)\ CH\ COOC_2H_5$$

It undergoes hydrolysis in two ways When boiled with alkalis, "acid hydrolysis" (I) takes place with the formation of oxalic acid, acetic acid, and alcohol On the other hand, boiling with dilute sulphuric acid brings about "ketonic hydrolysis" (II) into carbon dioxide and pyruvic acid When heated alone, carbon monoxide is evolved and malonic ester formed (III)

$$\begin{array}{ll} \text{I} & C_2H_5O_2C\ CO\ CH_2\ CO_2C_2H_5 \longrightarrow HO_2C\ CO_2H + CH_3\ COOH + 2C_2H_5OH \\ \text{II} & C_2H_5O_2C\ CO\ CH_2\ CO_2C_2H_5 \longrightarrow HO_2C\ CO\ CH_3 + CO_2 + 2C_2H_5OH \\ \text{III} & C_2H_5O_2C\ CO\ CH_2\ CO_2C_2H_5 \longrightarrow C_2H_5O_2C\ CH_2\ CO_2C_2H_5 + CO \end{array}$$

Acetone dicarboxylic acid, *β keto glutaric acid*, $HOOC\ CH_2\ CO\ CH_2\ COOH$, is obtained from citric acid by warming it with fuming sulphuric acid,

$$HO_2C\ CH_2\ C(OH)(CO_2H)\ CH_2\ CO_2H = HO_2C\ CH_2\ CO\ CH_2\ CO_2H + CO + H_2O$$

or by oxidation with permanganate It dissolves readily in water and in ether, and melts about 130° with decomposition into carbon dioxide and acetone Four of the hydrogen atoms in acetone dicarboxylic acid can be replaced by sodium, since each methylene group lies between two carbonyl groups

Oxalo succinic ester, $\begin{array}{ccccc} CO & — & CH & — & CH_2 \\ | & & | & & | \\ COOEt & & COOEt & & COOEt \end{array}$, is formed by condensing oxalic and succinic esters in the presence of sodium ethoxide It exists in two liquid modifications, of which one (enolic) gives a deep red coloration with ferric chloride and the other (ketonic) gives none [1]

Diaceto succinic ester is prepared by the action of iodine on sodium acetoacetic ester (see p 260) As has already been mentioned, it has proved of great service in the experimental investigation of tautomerism

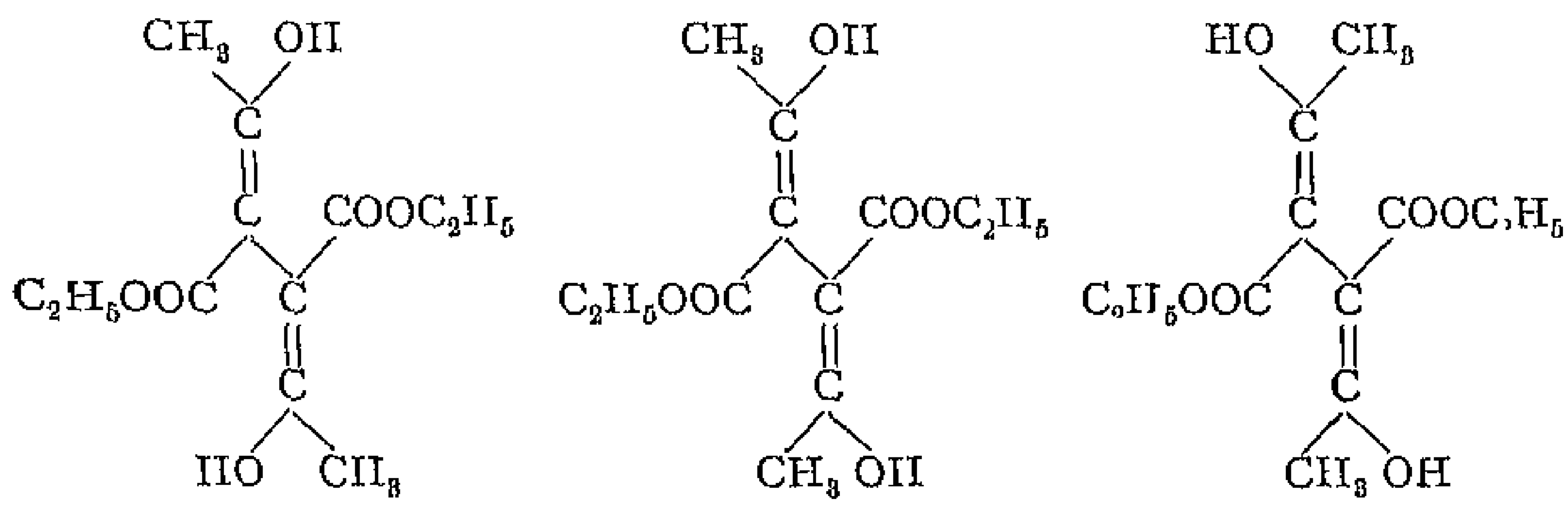
The compound exists in desmotropic modifications which may be ketonic (I) or enolic (II) in structure

$$\text{I}\quad \begin{array}{l} CH_3—CO—CH—COOC_2H_5 \\ \qquad\qquad\quad | \\ CH_3—CO—CH—COOC_2H_5 \end{array} \qquad \text{II}\quad \begin{array}{l} CH_3—C(OH)=C—COOC_2H_5 \\ \qquad\qquad\qquad\quad | \\ CH_3—C(OH)=C—COOC_2H_5 \end{array}$$

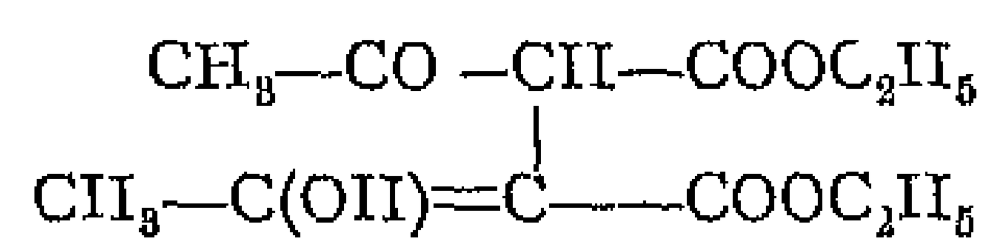
In diaceto-succinic ester, however, we have the possibility of other types of isomerism The ketonic form contains two similar asymmetric carbon atoms and should exist, like tartaric acid, in dextro, laevo-, racemic and meso-modifications In addition, the unsaturated enolic

[1] W Wislicenus and Waldmüller, *Ber*, 1911, 44, 1564

form would be expected to exhibit geometrical isomerism and to occur in the following three stereoisomeric varieties



Finally, there is the case in which both the ketonic and enolic structures may be united in the same molecule to give the mixed form,



opening up the possibility of six more isomerides, viz, the *cis* and *trans* compounds, each of which may be expected to occur in *d*-, *l*- and *i*- forms In all, thirteen different diaceto-succinic esters are to be expected from theoretical considerations

Up to the present five isomeric esters have been actually isolated, two optically inactive keto-forms (termed β- and γ esters respectively) and three enol-forms (α-, α_2- and α_3-esters) The enolic forms differ from the keto compounds in possessing weakly acidic character α- and α_2-esters give the characteristic ferric chloride reaction, α_3-, β- and γ-esters, on the contrary, do not

These different isomerides are only stable in the solid state In the fluid or dissolved state all five undergo change, so that, whatever form is started from, the final mixture contains all five modifications in proportions which vary with the conditions

In the cold this intramolecular change takes place so slowly that the relative amounts present in a homogeneous mixture can be estimated with sufficient accuracy by the mechanical separation of the components (*e g*, freezing out, followed by filtration) Numerous quantitative experiments carried out by Knorr have shown that the desmotropic diaceto-succinic esters, in the fused state or in solution, form a mixture of isomerides in equilibrium with one another Such a mixture has been called an allelotropic mixture

The examination of the diaceto-succinic esters has also shed more light on other cases of tautomerism, in which the changes occurring cannot be followed satisfactorily by existing methods A summary of the general conclusions arrived at by Knorr is given on p 63

XVII

Aldehydic and Ketonic Alcohols, Carbohydrates[1]

The carbohydrates are of the greatest importance from the theoretical as well as the practical standpoint. As foodstuffs they undoubtedly rank in the first place, and with the single exception of the proteins, no class of organic compounds is of such value in the study of the chemical processes which take place in plant and animal organisms. The term carbohydrate originally covered three groups of compounds, viz., those including glucose $C_6H_{12}O_6$, cane sugar $C_{12}H_{22}O_{11}$, and cellulose $(C_6H_{10}O_5)_n$ respectively. As may be seen from their formulæ, these substances are all composed of the three elements carbon, hydrogen and oxygen, united in characteristic manner. The number of carbon atoms is six or a multiple of six, and there are twice as many hydrogen atoms as oxygen atoms in the molecule. The last two elements are therefore present in the proportions required to form water, a peculiarity which gave rise to the term *carbohydrate*. Later, however, as the classical researches of Emil Fischer threw more light on the constitution of these compounds, and the great number of examples already known became increased by the addition of numerous synthetic products, the conception of the term carbohydrate had to be expanded and a new nomenclature introduced. Before going into the question in detail, it may be remarked that the carbohydrates of the glucose group, $C_6H_{12}O_6$, contain two hydrogen atoms less than the hexahydric alcohols, $C_6H_{14}O_6$ (see p. 246), and from their chemical character are divided into *aldehydic alcohols* and *ketonic alcohols*. A simpler example of an aldehydic alcohol is glycollic aldehyde, $CH_2OH \cdot CHO$, and of a ketonic alcohol, dihydroxy-acetone, $CH_2OH \cdot CO \cdot CH_2OH$.

The first division of the carbohydrates is into three main classes according to their complexity, viz.:

A. *Monosaccharides*, *e.g.*, arabinose, $C_5H_{10}O_5$, glucose, $C_6H_{12}O_6$.
B. *Di- and tri-saccharides*, *e.g.*, cane sugar, $C_{12}H_{22}O_{11}$, raffinose $C_{18}H_{32}O_{16}$.
C. *Higher polysaccharides*, *e.g.*, starch, cellulose, $(C_6H_{10}O_5)_n$.

Owing to their sweet taste and crystalline character the mono-, di- and trisaccharides are generally grouped together under the name of *sugars*. The character of a monosaccharide, originally associated with the presence of six carbon atoms in the molecule, is nowadays determined

[1] *Cf.* E. Fischer, "Synthesen in der Zuckergruppe" *Ber.*, 1890, 23, 2114. E. F. Armstrong, *The Simple Carbohydrates and the Glucosides* (Longmans, Green, 1924). W. N. Haworth, *The Constitution of Sugars* (Arnold, 1929).

mainly by its constitution as an aldehydic alcohol containing the group $-CHOH\cdot CH:O$, or as a ketonic alcohol with the group $-CO\cdot CH_2OH$ In this class are included not only those compounds with six carbon atoms, but many with a smaller or greater number than this A further distinction is drawn between aldehydic and ketonic sugars by use of the terms *aldoses* and *ketoses* The number of oxygenated carbon atoms present in the molecule is indicated by adding the necessary prefix to the termination *-ose* In this way monosaccharides are subdivided into the smaller classes of *bioses, trioses, tetroses, pentoses, hexoses, heptoses, octoses and nonoses* Since, however, the members of these groups may be either aldehydes or ketones, this is expressed by use of the prefix *aldo-* or *keto-* respectively For example, glyceric aldehyde, $CH_2OH\cdot CHOH\cdot CHO$, is an *aldotriose*, and dihydroxy-acetone, $CH_2OH\cdot CO\cdot CH_2OH$, a *ketotriose*

The polysaccharides appear to be anhydrides or ether derivatives of the monosaccharides If they are formed from 2 mols of the monosaccharide by loss of 1 mol water they are termed *disaccharides*, *e g* cane sugar, $C_{12}H_{22}O_{11}$ Raffinose, $C_{18}H_{32}O_{16}$, is a *trisaccharide* formed from three monosaccharide molecules by elimination of 2 mols water Generalising these formulæ we obtain $nC_6H_{12}O_6-(n-1)H_2O$ If n is very large, the factor $n-1$ approximates to n, and we have

$$nC_6H_{12}O_6-nH_2O=n(C_6H_{12}O_6-H_2O)=n(C_6H_{10}O_5)$$

The latter is the formula for the higher polysaccharides, including starch and cellulose All polysaccharides undergo hydrolysis, taking up water to form monosaccharides

I —MONOSACCHARIDES[1]

The number of monosaccharides known is in the neighbourhood of fifty, of which ten occur in nature and the remainder are synthetic The existence of such a large number of compounds is due to the presence of asymmetric carbon atoms within the molecules Aldohexoses, for example, which include glucose, a sugar of great historical and practical interest, contain no less than four asymmetric atoms, each of which may be present in either the *d-* or *l-* configuration It has already been shown on p 35 how rapidly the number of stereo isomerides increases with each additional asymmetric atom

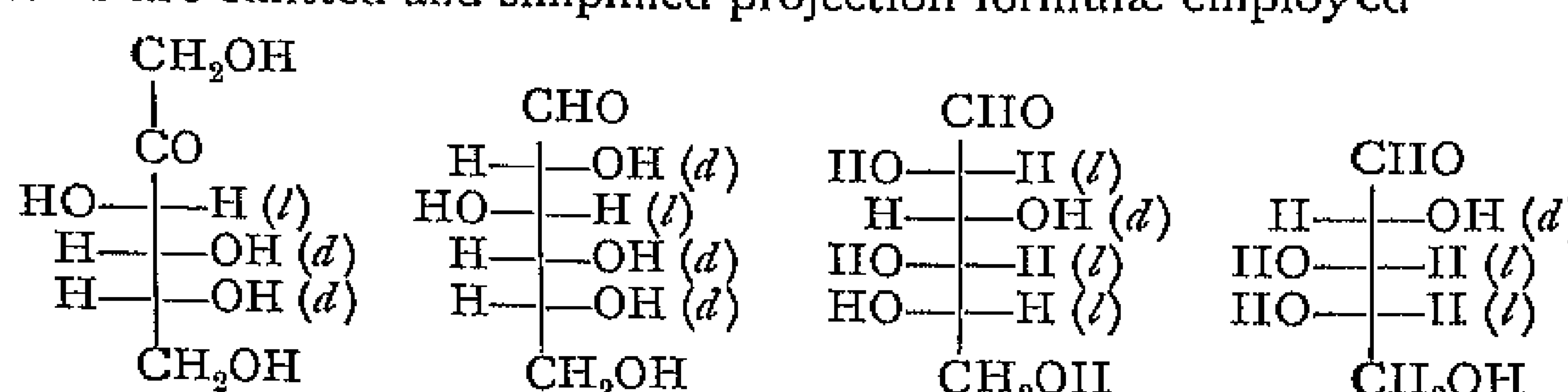
A list of the best known monosaccharides is given below

Biose	$CH_2OH\cdot CHO$, glycollic aldehyde
Trioses	1 $CH_2OH\cdot CHOH\cdot CHO$, glyceric aldehyde
	2 $CH_2OH\cdot CO\cdot CH_2OH$, dihydroxy acetone
Tetroses	Erythrose, probably a mixture of $CH_2OH\cdot(CHOH)_2\cdot CHO$ and $CH_2OH\cdot CHOH\cdot CO\cdot CH_2OH$
Pentoses	$CH_2OH\cdot(CHOH)_3\cdot CHO$, arabinose, xylose, ribose

[1] For the connection between the constitution of aliphatic compounds and their sweetness of taste, see E Oertly and R G Myers, *J Am C S*, 1919, **41**, 855

Methyl pentose	CH_3 (CHOH)$_4$ CHO, rhamnose
Hexoses	1 CH_2OH (CHOH)$_4$ CHO, glucose, gulose, mannose, galactose, talose
	2 CH_2OH (CHOH)$_3$ CO CH_2OH, fructose, sorbose
Heptoses	CH_2OH (CHOH)$_5$ CHO, mannoheptose, glucoheptose, galaheptose
Octoses	$C_8H_{16}O_8$
Nonoses	$C_9H_{18}O_9$

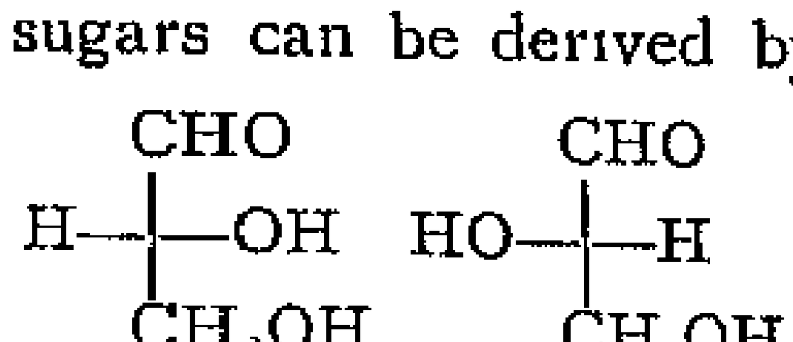
An explanation is required as to the way in which the optical isomerides are named In accordance with a suggestion of Fischer, the structure of the sugars is, wherever possible, referred back to that of the active glucoses Any other monosaccharide standing in close structural relationship to one or other of the glucoses is generally labelled with the corresponding letter *d*- or *l*-, irrespective of the actual sign of its rotation Ordinary fructose, for example, which is lævorotatory, is commonly termed *d*-fructose, owing to its spatial relationship to *d* glucose, and naturally occurring arabinose, which is dextrorotatory, is termed *l* arabinose to indicate its relationship to *l*-glucose This is illustrated in the following formulæ, in which the terminal aldehydic or ketonic group is written uppermost, according to the usual convention a CHOH-group having the hydroxyl on the right of the formula is then regarded as being of the *d*-configuration and *vice versa* In the following pages the asymmetric carbon atoms are omitted and simplified projection formulæ employed



d fructose *d* glucose *l*-glucose *l*-arabinose

In some cases the actual sign of the rotation given by a compound is indicated in the following pages by the use of the signs + and −, *e g* *d*(−)-fructose for ordinary fructose In addition, the prefix *dl*- indicates a racemic and *i*- a meso form

Wohl's work on glycerose now enables the family relationships to be carried back to the *d*- and *l*-glyceroses, from which all other sugars can be derived by extending the molecule on the side of the aldehyde group by reaction with HCN (see p 292) The nomenclature fortunately remains unchanged, as *d*-glycerose is *d*-rotatory and is *genetically related* to *d*-glucose Hence it will be seen that the family of a sugar is determined in each case by the spatial arrangement of the CHOH-group adjacent to the terminal CH_2OH, no matter what the disposition



d glycerose *l* glycerose

of the rest of the molecule may be (*cf* table on p 301) If this group has a dextro configuration, as indicated by writing it with the OH to the right, the sugar is classified as belonging to the *d*-family

The same system is applied to other derivatives of the monosaccharides

General Properties and Methods of Formation

The monosaccharides are sweet-tasting compounds, the chemical behaviour of which may be deduced from their structure as aldehydic or ketonic alcohols

As alcohols they unite readily with acids to form *esters*, *e g*, acetic anhydride converts them into acetyl derivatives, and with nitric acid at 0° they form nitrates The *phosphoric esters of pentoses and hexoses* are of great physiological importance, the former as disruption products of many nucleic acids (p 771) and the latter as being essential for the biological degradation of carbohydrates, *e g* in alcoholic fermentation and during muscular effort[1] (see p 314) With inorganic bases the monosaccharides yield *alcoholates*, those from glucose, for example, being known as glucosates

As aldehydes or ketones they are characterised by numerous reactions, only the more important of which need be quoted On *reduction* they take up two atoms of hydrogen and pass into the corresponding alcohols, from a pentose is obtained a pentitol or pentahydric alcohol, and from a hexose a hexitol or hexahydric alcohol On *oxidation* they yield carboxylic acids Cautious oxidation converts aldoses first into the corresponding monocarboxylic acids containing the same number of carbon atoms, aldopentoses being transformed into pentonic acids, $CH_2OH \cdot (CHOH)_3 \cdot COOH$, and aldohexoses into hexonic acids, $CH_2OH \cdot (CHOH)_4 \cdot COOH$ With stronger oxidising agents the process may go further and hexoses, for example, may be oxidised to the corresponding stereo-isomeric saccharic or tetra-hydroxy-adipic acids, $COOH \cdot (CHOH)_4 \cdot COOH$ As would be expected, the ketoses on oxidation yield acids containing a smaller number of carbon atoms The *reducing properties* of the monosaccharides are shown in their behaviour with ammoniacal silver nitrate solution, from which silver is precipitated, and particularly with Fehling's solution, from which on warming a reddish precipitate of cuprous oxide is thrown down In the absence of other reducing agents, the last reaction may be employed not only for the qualitative detection of the monosaccharides, but also for their quantitative estimation

Some of the more important processes which have been devised for studying the relationships among the simpler carbohydrates are described in the following pages

[1] Compare B A Harden and W J Young, *Proc Chem Soc*, 1905, **21**, 189 G Embden and M Zimmermann, *Zeit physiol Chem*, 1927, **167**, 114

Osazones and the Conversion of Aldoses into Ketoses

As aldehydes or ketones the monosaccharides also react with hydrazines and hydroxylamine. *Phenyl-hydrazine*, $C_6H_5NHNH_2$, has proved of the greatest value in the separation, identification and interconversion of the various monosaccharides. Without the aid of this reagent the brilliant researches of Fischer in the sugar group would hardly have been possible.

When 1 mol. of phenyl-hydrazine reacts with 1 mol. of an aldose or ketose, the first product is a normal hydrazone (see p. 172):

$$\underset{\text{Glucose}}{CH_2OH[CH.OH]_4.CH:O} + H_2N.NHC_6H_5$$
$$= \underset{\text{Glucose phenyl-hydrazone}}{CH_2OH[CH.OH]_4.CH:N.NHC_6H_5} + H_2O$$

On warming with excess of phenyl-hydrazine, however, the hydrazone first formed is oxidised in such a way that the CH.OH group adjacent to the original aldehydic or ketonic group is converted into a CO group.[1] The latter then combines with more phenyl-hydrazine to give a di-hydrazone containing the group I. These compounds are termed **osazones**.

$$\text{I}\quad \begin{array}{l} CH:N.NH.C_6H_5 \\ | \\ C:N.NH.C_6H_5 \\ | \end{array} \qquad\qquad \begin{array}{l} CH:N.NH.C_6H_5 \\ | \\ C:N.NH.C_6H_5 \\ | \\ (CHOH)_3 \\ | \\ CH_2OH \end{array} \quad \text{Glucosazone}$$

Prior to Fischer's researches one of the greatest barriers to a wider knowledge of the monosaccharides lay in the difficulty of separating mixtures of these sugars by crystallisation, owing to their high solubility in water and tendency to form syrups. The value of the osazones depends on the fact that they are sparingly soluble, and easily separable by crystallisation, and, in addition, from their characteristic melting-points and crystalline forms it is possible to identify the parent sugar with ease and certainty.

The *recognition and isolation of ketoses* is a matter of some difficulty owing to their lack of characteristic reactions. With secondary hydrazines of the type of phenyl-methyl hydrazine, however, the ketoses give phenyl methyl osazones by which they may be identified (Neuberg, *Ber.*, 1902, 35, 959, 2626). Aldoses only react with this base to form colourless hydrazones, which in all cases are easily distinguished or separated from the highly coloured osazones.

Osazones, like all hydrazones, are hydrolysed on being heated with

[1] In this reaction phenyl hydrazine removes two atoms of hydrogen from the sugar and is converted into aniline and ammonia: $C_6H_5.NH.NH_2 + 2H = C_6H_5.NH_2 + NH_3$.

hydrochloric acid, when phenyl-hydrazine is regenerated. The sugar originally employed, however, is not regained, but the group

$$-C(:N \cdot NH \cdot C_6H_5)-CH(:N \cdot NH \cdot C_6H_5)$$

is converted into the group $-CO \cdot CHO$. The compound so formed is an oxidation product of the original sugar, and is termed an **osone**. In the example quoted above glucose yields

$$\underset{\text{Glucosone}}{CH_2OH(CHOH)_3 \cdot CO \cdot CHO}$$

On mild reduction of this compound the aldehydic group alone is attacked and converted into an alcoholic group, the keto group remaining unchanged. In this case, therefore, the sugar finally obtained is fructose, in place of the glucose used as starting material.

$$\underset{\text{Fructose}}{CH_2OH \cdot (CHOH)_3 \cdot CO \cdot CH_2OH}$$

In these reactions we have a *general method of transforming an aldose into a ketose*, according to the scheme

$$\text{Aldose} \xrightarrow[\text{Hydrazine}]{\text{Phenyl}} \text{Osazone} \xrightarrow{\text{Hydrolysis}} \text{Osone} \xrightarrow{\text{Reduction}} \text{Ketose}$$

Degradation and Synthesis of Aldoses

Monosaccharides react with hydroxylamine to yield oximes, the aldehydic or ketonic oxygen being replaced by the group $:N \cdot OH$. By means of these compounds it is possible to bring about the *degradation of a higher aldose to one of lower carbon content*. For example, glucose forms the oxime $CH_2OH \cdot (CHOH)_4CH:NOH$, which on being heated with acetic anhydride parts with water and is converted into the acetyl derivative of the nitrile $CH_2OH(CHOH)_4CN$. The latter on treatment with ammoniacal silver nitrate is decomposed, yielding hydrogen cyanide and the corresponding aldopentose, *d*-arabinose.

$$CH_2OH \cdot (CHOH)_3 \cdot CHOH \cdot CN \longrightarrow HCN + CH_2OH \cdot (CHOH)_3 \cdot CH:O$$

Aldoses may also be degraded by converting them into the corresponding monobasic acids, *e.g.* $CH_2OH \cdot (CHOH)_4 \cdot COOH$, and oxidising the latter in the form of their calcium salts with hydrogen peroxide and a trace of a ferric salt (*Fenton's reagent*). In this reaction the carboxyl group is eliminated as carbon dioxide, and at the same time the adjacent alcoholic group is oxidised to aldehyde.

$$CH_2OH \cdot (CHOH)_3 \cdot CHOH \cdot COOH + O \\ \longrightarrow CH_2OH \cdot (CHOH)_3 \cdot CHO + CO_2 + H_2O$$

Monosaccharides, as aldehydes and ketones, also unite with hydrogen cyanide to form cyanhydrins. By use of this reaction we may effect the *synthesis of a higher from a lower aldose*. The

cyanhydrins are first hydrolysed to hydroxy acids, which are readily converted into lactones The latter are then reduced to aldoses by means of sodium amalgam and dilute sulphuric acid Glucose, $C_6H_{12}O_6$, under these conditions yields a new sugar, $C_7H_{14}O_7$

$$\underset{\text{Glucose}}{CH_2OH\ [CHOH]_4\ CH\ O} + HCN \longrightarrow \underset{\text{Glucose cyanhydrin}}{CH_2OH\ [CHOH]_4\ CHOH\ CN}$$

$$\xrightarrow{\text{Hydrolysis}} \underset{\text{Glucose carboxylic acid}}{CH_2OH\ CHOH\ CHOH\ CHOH\ CHOH\ CHOH\ COOH} \xrightarrow{-H_2O}$$

$$\underset{\text{Lactone of glucose carboxylic acid}}{CH_2OH\ CHOH\ CHOH\ \underbrace{CH\ CHOH\ CHOH\ CO}_{O}}$$

$$\xrightarrow{2H} \underset{\text{Gluco heptose}}{CH_2OH\ CHOH\ CHOH\ CHOH\ CHOH\ CHOH\ CH\ O}$$

In a similar manner gluco-heptose may be used to build up an octose The synthesis has been carried as far as the nonoses

Conversion of Ketoses into Aldoses

In this connection a series of reactions may be mentioned by means of which it is possible to pass from *ketoses into aldoses* The ketose is reduced to the corresponding alcohol, which on oxidation yields a monobasic acid This in turn readily passes into the lactone, from which an aldose is obtained by reduction, *e g*

$$\underset{\text{Ketohexose}}{CH_2OH(CHOH)_3\ CO\ CH_2OH} \xrightarrow{\text{Reduction}} \underset{\text{Hexitol}}{CH_2OH(CHOH)_3\ CHOH\ CH_2OH}$$

$$\xrightarrow{\text{Oxidation}} \underset{\text{Hexonic acid}}{CH_2OH(CHOH)_3\ CHOH\ COOH}$$

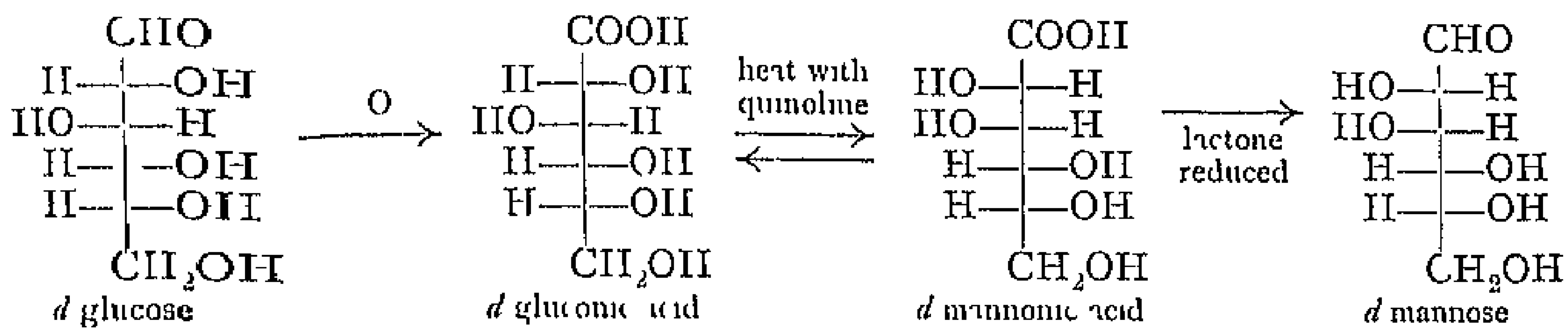
$$\xrightarrow{H_2O\ \text{eliminated}} \underset{\text{Lactone of the hexonic acid}}{CH_2OH\ CHOH\ \underbrace{CH\ CHOH\ CHOH\ CO}_{O}}$$

$$\xrightarrow{\text{Reduction}} \underset{\text{Aldohexose}}{CH_2OH\ (CHOH)_3\ CHOH\ CH\ O}$$

Epimerisation

In synthetic work with the aldoses considerable use has been made of a process termed *epimerisation*, which reverses the configuration of the CHOH-group in the α position to the terminal aldehyde grouping (*cf* p 38) The aldose is first oxidised to the corresponding mono-carboxylic acid, which is then heated with aqueous quinoline or pyridine, when the inversion of the α-group is more or less completely effected On converting the new acid into the corresponding lactone, followed

by reduction, a new aldose is obtained. This process may be illustrated by the transformation of glucose into mannose:



In this manner a number of new aldoses have been prepared.

Other Reactions of Sugars

With the aid of the Grignard reaction hydrocarbon radicals may be added to the sugar molecule.[1]

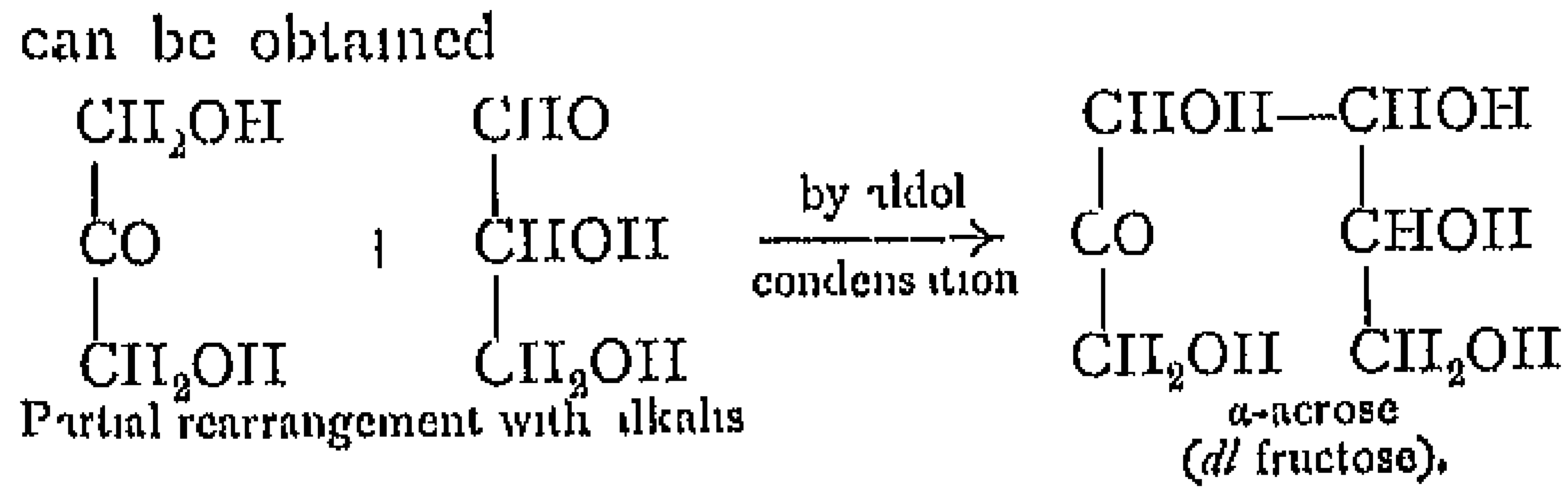
On warming with alkalis the monosaccharides give yellowish-brown solutions and finally resinify.

The presence of a sugar can often be determined qualitatively by certain colour reactions. Among these may be mentioned the *formation of furfural* (see index) by the action of heat on any monosaccharide in the dry state. If a paper previously treated with aniline acetate is held in the escaping vapours, it develops a red coloration.

Molisch's test is also a general one. This consists in adding to the sugar solution one or two drops of a solution of α-naphthol, and pouring down the side of the vessel a little concentrated sulphuric acid (free from nitric acid). The furfural derivatives formed by the action of sulphuric acid produce a violet coloration at the junction of the two liquids, either in the cold or on gentle warming.

Monosaccharides have been prepared artificially by the following methods:

1. A valuable starting point for the synthesis of natural sugars was discovered by E. Fischer in glycerol. On careful oxidation with nitric acid, or with bromine water and sodium carbonate, glycerol yields a product which gives the reactions of the monosaccharides and is therefore known as *glycerose*. Among other constituents this substance contains a large proportion of *dihydroxy-acetone*, $CH_2OH \cdot CO \cdot CH_2OH$. Under the influence of dilute alkalis glycerose condenses to a ketohexose, *α-acrose* or *dl*-fructose, from which both glucose and fructose can be obtained.



[1] Paal, *Ber.*, 1906, 39, 1361, 2823; 1911, 44, 3543.

Aldoses and ketoses may also be formed quite generally by oxidation of the corresponding alcohols (for example, with nitric acid, sodium hypobromite, hydrogen peroxide and ferrous sulphate, or lead peroxide and hydrochloric acid). In this way arabinose, $C_5H_{10}O_5$, may be obtained from arabitol $C_5H_{12}O_5$, and mannose from mannitol.

2. The same α-acrose that is formed from glycerose can also be prepared from formaldehyde. On allowing the latter to remain in contact with lime-water it undergoes the aldol condensation (see p. 171), and amongst other compounds a mixture of sugars of the formula $C_6H_{12}O_6$ is produced, known as *formose*, from which α-acrose may be isolated.

$$H_2C{:}O + HCH{:}O + HCH{:}O + HCH{:}O + HCH{:}O + HCH{:}O$$
$$= H_2C{\cdot}OH{-}CH{\cdot}OH{-}CH{\cdot}OH{-}CH{\cdot}OH{-}CH{\cdot}OH{-}CH{:}O$$

3. The formation of monosaccharides by the hydrolysis of polysaccharides with dilute acids has been mentioned on p. 287, *e.g.*

$$C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$$

4. Higher aldoses may be built up from lower members by the cyanhydrin method (see p. 292).

Sugars prepared by complete synthesis in the laboratory are always first obtained in an optically inactive form, whereas those produced in plants by the assimilation of carbon dioxide are active. Laboratory methods, however, also yield active products if optically active materials take part in the reaction (see asymmetric synthesis, p. 46). This is what occurs in the natural process, since the conversion of carbonic acid into sugar is undoubtedly brought about in collaboration with the optically active substances of the chlorophyll nucleus. There is therefore no fundamental difference between the artificial and natural synthesis of optically active compounds.

1. Bioses, Trioses and Tetroses

The simplest example of this group is **glycollic aldehyde**, $CH_2OH{\cdot}CHO$, which can be obtained from glycol by oxidation with hydrogen peroxide, or from bromo-acetaldehyde, $CH_2Br{\cdot}CHO$, by treatment with baryta. It is a syrup of somewhat sweet taste. The two trioses, **glyceric aldehyde** and **dihydroxy acetone**, have already been mentioned (pp. 244, 293). The former is prepared by oxidation of acrolein acetal and hydrolysis of the resulting acetal of glyceric aldehyde. It occurs in a stable dimolecular form, m.p. 138°, which in aqueous solution is slowly transformed into an enolic syrupy monomolecular form.[1] *Dihydroxy acetone* is a crystalline compound, m.p. 68-75°, which is soluble in water and has a sweet taste. With sodium amalgam it is readily reduced to glycerol.

Glycollic aldehyde and glyceric aldehyde differ from higher aldoses in the ease with which they polymerise to compounds of twice their molecular weight. In other ways also the aldehydic character is more pronounced than with the higher sugars. Among the tetroses, *dl* **erythrose** is obtained by oxidation of the corre-

[1] Wohl, *Ber.*, 1898, **31**, 1796, 2394. See also H. G. Reeves, *J. C. S.*, **1927**, 2477.

sponding alcohol *i e* erythritol, and by the condensation of glycollic aldehyde In the former case the product consists mainly of a mixture of aldotetrose and ketotetrose, in the latter case the aldotetrose is probably formed

Additional methods of preparing tetroses include the *degradation of pentoses* by way of the oximes (see p 291), and the *oxidation of pentonic acids* (in the form of their calcium salts) with hydrogen peroxide in the presence of a trace of ferric salt (p 291)

2 Pentoses

Aldopentoses of the formula

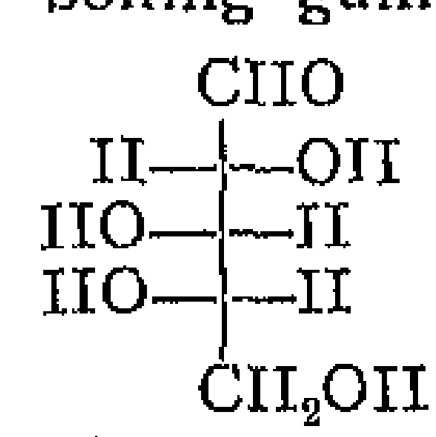
$$CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHO$$

contain three asymmetric carbon atoms, and according to theory should therefore exist in eight optically active and four racemic forms Two of these, l-*arabinose* and d-*xylose*, occur in the combined state in the vegetable kingdom in the complex polysaccharides pentosans, and in the form of glucosides d-*ribose* is found as a constituent of the nucleoproteins (p 770) These naturally occurring sugars are described below Other pentoses have been prepared synthetically

In their chemical behaviour pentoses possess the general properties of the monosaccharides, but in addition give characteristic reactions by which they are easily recognised and distinguished from hexoses For example, when heated with diluted hydrochloric or sulphuric acid they yield *furfural*, $C_5H_4O_2$, (methyl pentoses give methyl furfural), which forms sparingly soluble derivatives with phenyl-hydrazine, pyrogallol, phloroglucinol and barbituric acid This reaction is used in the quantitative estimation of pentoses[1] A qualitative test for pentoses consists in heating them with *hydrochloric acid and phloroglucinol*, when a cherry-red coloration is produced

The pentoses do not undergo fermentation

l(+)**Arabinose**,[2] is obtained together with xylose by boiling gum arabic, cherry gum, or the pith of maize and elder with dilute sulphuric acid (hydrolysis of pentosans) It forms prisms, m p 160°, and is dextrorotatory On reduction it yields l-*arabitol*, and on oxidation passes first into l *arabonic acid*, $CH_2OH \cdot (CHOH)_3 \cdot COOH$, and finally into l-*trihydroxy-glutaric acid*, $COOH \cdot (CHOH)_3 \cdot COOH$

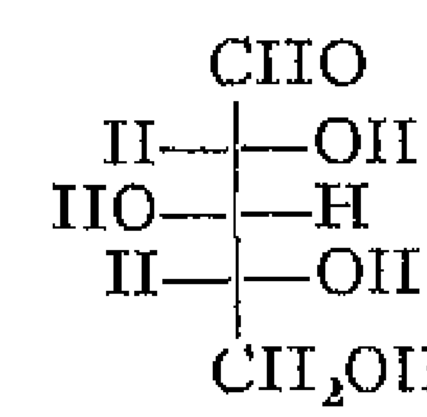


l-Arabinose

d(−)**Arabinose**, the optical antipode of the above compound, is produced by the degradation of *d* glucose oxime or of *d* gluconic acid *dl* **Arabinose**, m p 164°, is formed by combination of the two optically active components and is possibly the pentose which is present in human urine in cases of pentosuria

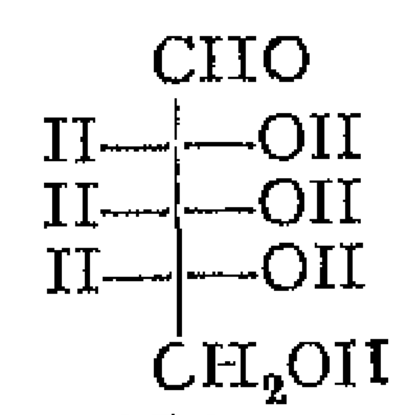
[1] *Ber*, 1902, 35, 4440 Jolles, *Ann*, 1907, 351, 38 For furfural, see index [2] For further information concerning the methods by which the configurations of the pentoses and hexoses have been derived, see Cohen, *Organic Chemistry*, Part III (Arnold), Armstrong, *The Simple Carbohydrates and the Glucosides* (Longmans, 1924), Haworth, *The Constitution of Sugars* (Arnold, 1929)

d-**Xylose**, or wood sugar, can be obtained from a variety of vegetable products, *e g* by boiling bran, wood or straw with dilute acids It is best prepared from maize cobs[1] It is dextrorotatory, and on reduction yields *i*-xylitol When oxidised it gives first *d*-xylonic acid and finally *i*-trihydroxy-glutaric acid *d*-Xylose is also formed by the degradation of *d* gulonic acid, and by synthetic methods may be converted into *d*-gulose When degraded through the oxime it yields *d*-threose, which is oxidisable to *l*-tartaric acid These reactions lead to the above configuration for *d*-xylose



d Xylose

d-**Ribose** is present in certain nucleic acids[2] (p 771) It forms the same osazone as *d* arabinose, and therefore has the configuration given

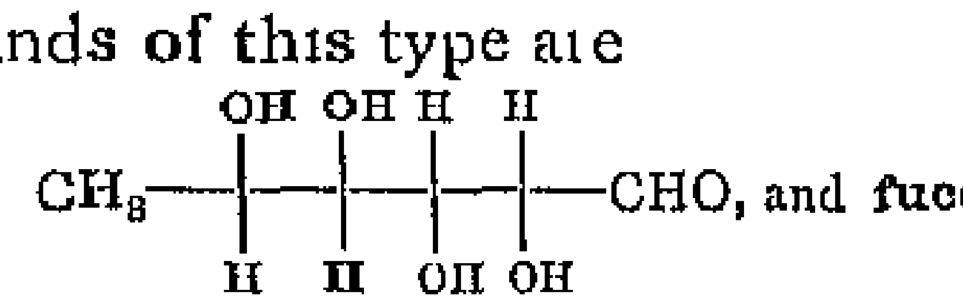
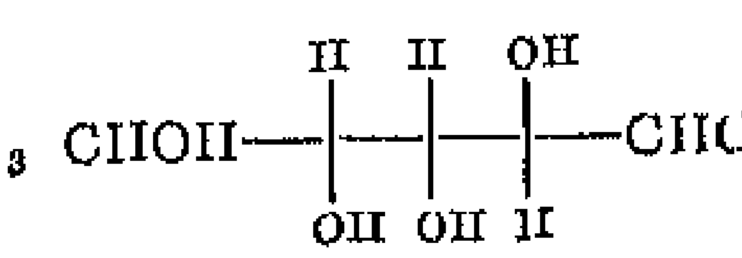


d-Ribose

Arabinose and xylose exhibit mutarotation (see p 88), *i e*, the rotation of a freshly prepared solution changes with time until a constant value is attained In both these cases the rotation diminishes An explanation of this peculiarity is given on p 299

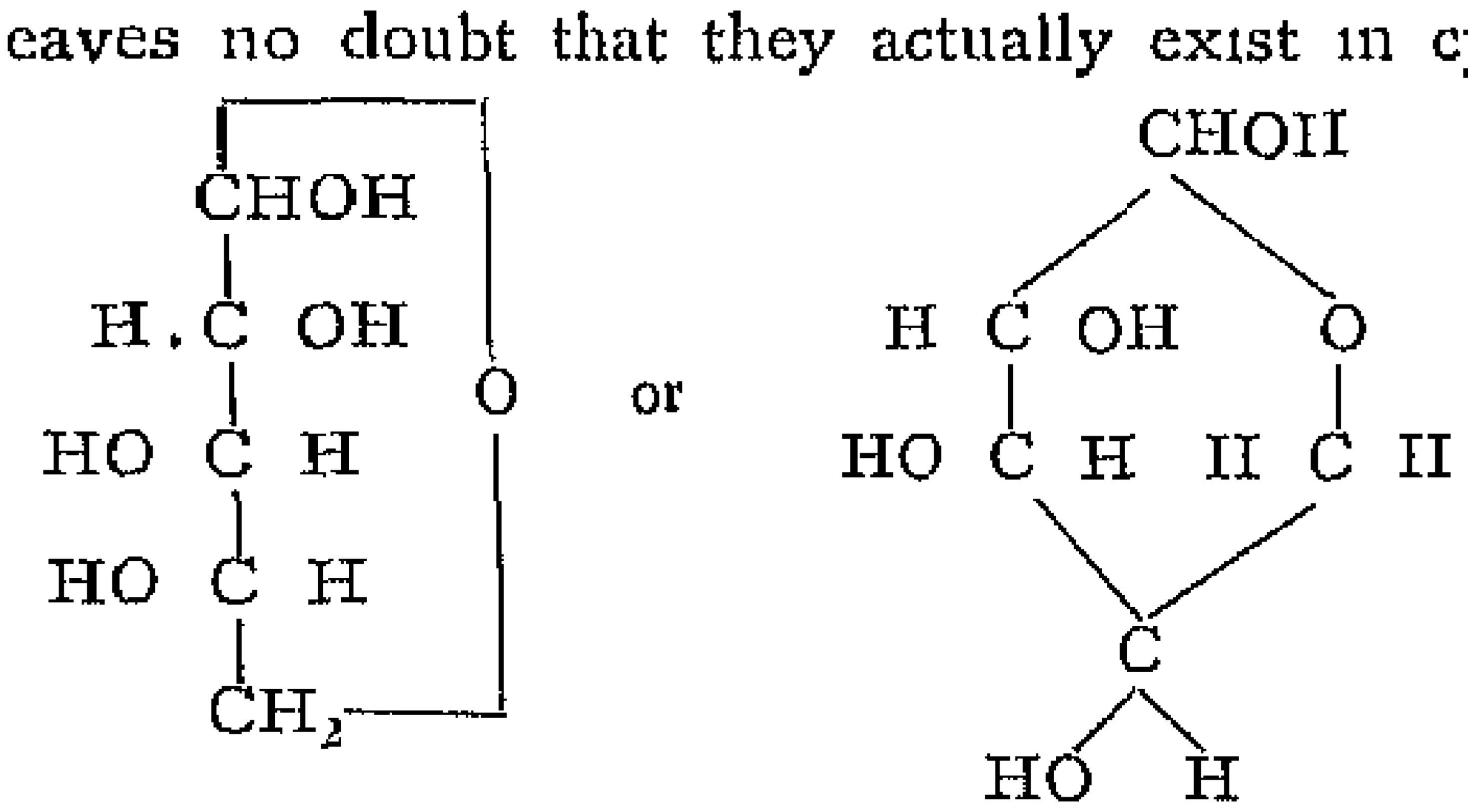
Other widely distributed members of this group are the *methyl-pentoses*, which are found in polysaccharides and glucosides of vegetable origin

Compounds of this type are

rhamnose  and **fucose** 

Rhamnose occurs in many glucosides and has played an important part in connection with the stereo-chemistry of sugars The question of its configuration has been settled by Fischer and Zach's synthesis of *iso*-rhamnose,[3] the first synthesis of a methyl-pentose to be effected Fucose is a constituent of many vegetable polysaccharides

For simplicity of presentation the pentoses have been represented in the foregoing pages as open chain sugars The work of Haworth, however, leaves no doubt that they actually exist in cyclic structures



l-Arabinose

[1] K P Monroe, *J Am C S*, 1919, **41**, 1002 [2] Levene and Jacobs, *Ber*, 1909, **42**, 1476
[3] *Ber*, 1912, **45**, 3761

of the other type containing a 6-membered ring (see p 299) *l*-Arabinose is therefore more correctly formulated by either of the structures at the bottom of the previous page, in which, as before, a CHOH group of the dextro configuration is written with the OH to the right

3 The Hexoses and Glucosides

Cyclic Structure of Monosaccharides

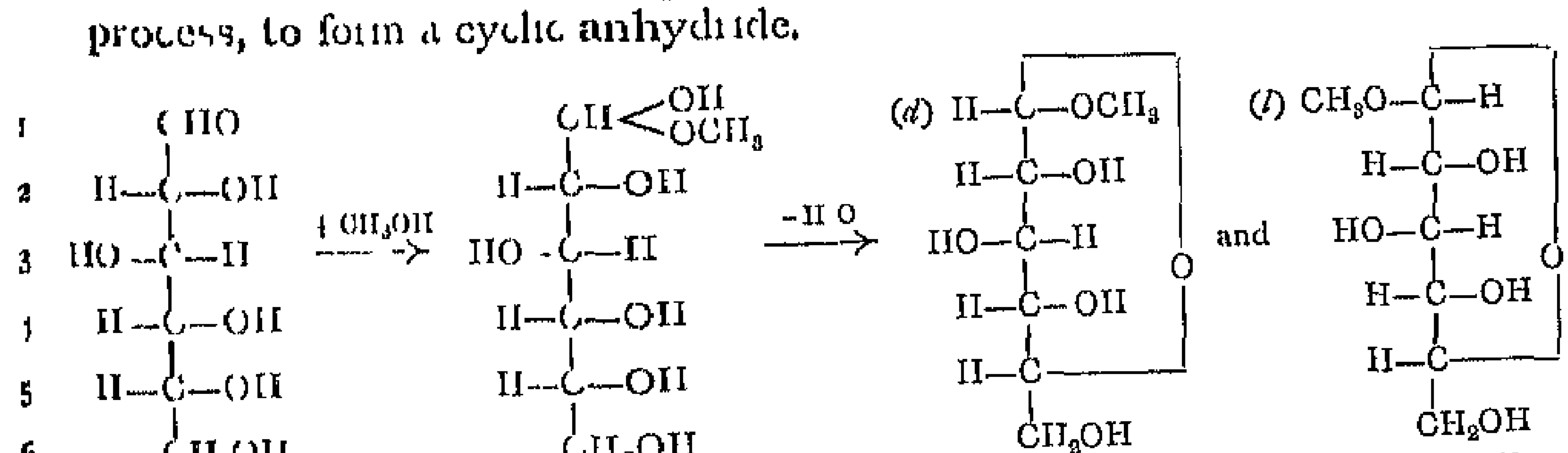
Hexoses are compounds of sweet taste, which are generally difficult to obtain in the crystalline state They are very soluble in water, sparingly soluble in absolute alcohol, and insoluble in ether The study of this group provided an admirable opportunity of putting stereochemical theory to an exacting test, from which it has emerged unscathed

The **aldohexoses**, $CH_2OH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHOH \cdot CHO$, contain four asymmetric atoms, and according to theory should exist in sixteen optically active isomerides, consisting of eight pairs of enantiomorphs In the table on p 301 will be found the configurational formulae of fourteen known aldohexoses, and two as yet undiscovered isomerides It is now generally accepted that each of these stereoisomerides normally exists in a cyclic form having an oxidic or inner ether structure Information on this point has been gathered chiefly from two sources, namely the study of glucosides and the researches on methylated sugars which were initiated many years ago by Purdie and developed with conspicuous success by Irvine and Haworth

A hexose such as glucose combines with methyl alcohol in the presence of hydrogen chloride to form a mixture of two stereoisomeric methyl-glucosides[1] These compounds do not react with phenylhydrazine and hence contain no free aldehyde group Although

$$C_6H_{12}O_6 + CH_3OH = C_6H_{11}O_5 \cdot OCH_3 + H_2O$$

comparatively stable towards alkalis, they are readily hydrolysed by hot dilute acids It is evident therefore that the aldehyde group is now united to alcohol in the same manner as in the acetals (see p 169) But since only one molecule of alcohol enters into combination with a molecule of glucose, with loss of one molecule of water, it must be assumed that an alcoholic group of the sugar also takes part in the process, to form a cyclic anhydride.



Possible intermediate compound

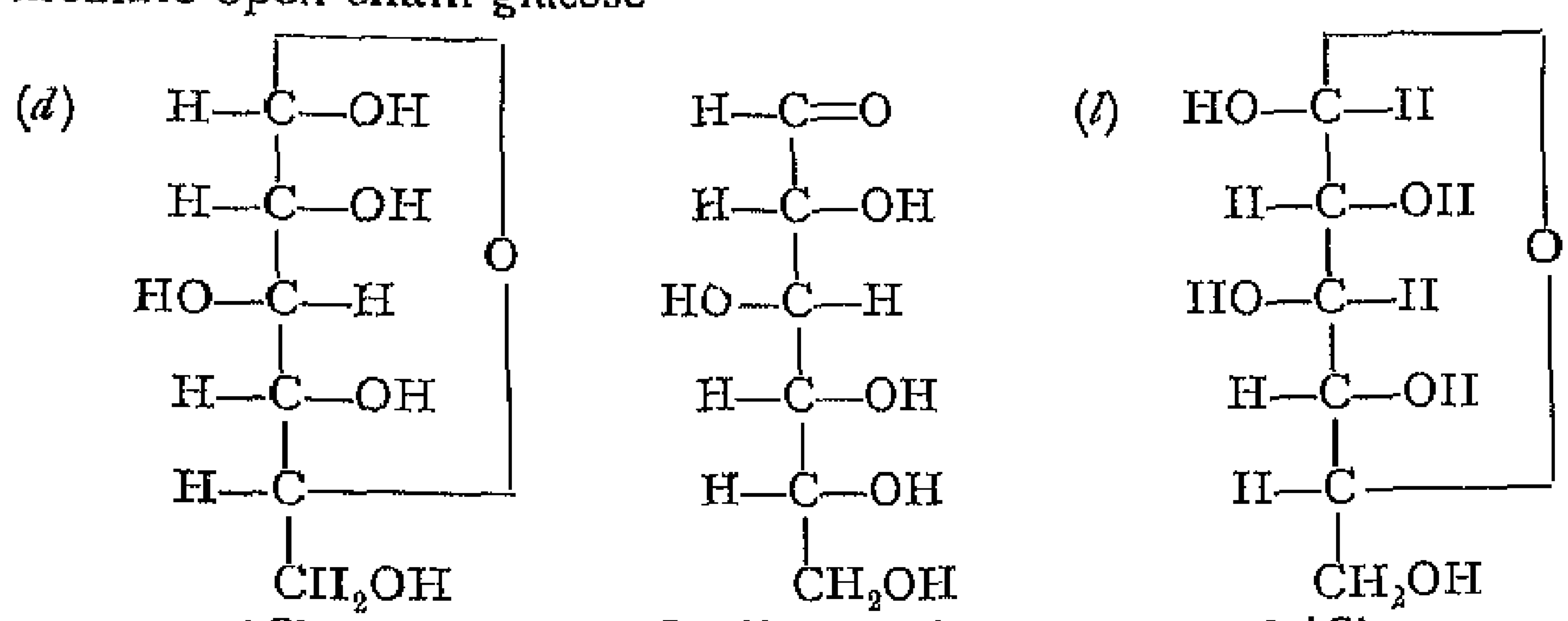
α Methyl glucoside $[\alpha]_D + 158$

β Methyl glucoside $[\alpha]_D - 34$

[1] E. Fischer, *Ber.*, 1893, 26, 2400.

It will be seen that the end carbon atom (1) has now become asymmetric and can thus exist in either the *d*- or *l*-configuration. There will therefore be two stereoisomeric glucosides, which are distinguished as the α- and β-forms. The actual hydroxyl group engaged in ring-formation was extremely difficult to identify with certainty, and until recently it was assumed, by analogy with the lactones of γ-hydroxy acids, that the union was to the C-atom in position 4. A cyclic structure of this kind is described as containing a butylene oxide or 1 : 4 oxidic ring.[1] Later research has shown that these compounds actually contain a 1 : 5- or amylene oxide link as illustrated in the above formulæ.

The behaviour of glucose in undergoing mutarotation led to the suggestion that the free sugar also occurred in cyclic forms corresponding to the α- and β-glucosides, and that mutarotation was due to the partial conversion of one form into the other through an intermediate open-chain glucose.



α *d*-Glucose $[\alpha]_D$ + 110° | Possible intermediate form | β *d* Glucose $[\alpha]_D$ + 17.5°

Definite proof of the existence of α- and β-glucoses was first obtained by E. F. Armstrong.[2] In common with other α- and β-glucosides, the methyl glucosides show characteristic differences in their behaviour towards certain hydrolytic enzymes. *Maltase* rapidly hydrolyses α-methyl glucoside in aqueous solution to methyl alcohol and glucose, but has no influence on the β-glucoside. On the other hand, the latter is readily hydrolysed by the enzyme *emulsin*, which however does not attack the α-compound. By this means glucosides have been classified as α- and β-glucosides, according to their behaviour towards these enzymes. Armstrong demonstrated the existence of a similar isomerism in the free sugar by showing that two glucoses of different rotatory powers were formed when α- and β-methyl glucosides respectively were hydrolysed by enzymes. The α-glucose liberated from the α-glucoside has a high rotation whereas β-glucose from the β-glucoside has a very low value. In a short time, or more

[1] This inner ether or lactone structure was first suggested by Tollens. [2] E. F. Armstrong, *J. C. S.*, 1903, 85, 1306. Lowry, *J. C. S.*, 1904, 87, 1551.

rapidly on addition of ammonia, each of the newly liberated forms changes into the same equilibrium mixture of α- and β-glucoses having a rotation of intermediate value. Hence the mutarotation of glucose is due to intramolecular change. Subsequently it was found that by recrystallising ordinary glucose under suitable conditions (p. 303) it is possible to convert it into the pure α- and β-glucoses, the rotations of which (prior to mutarotation) are appended to the above formulæ.

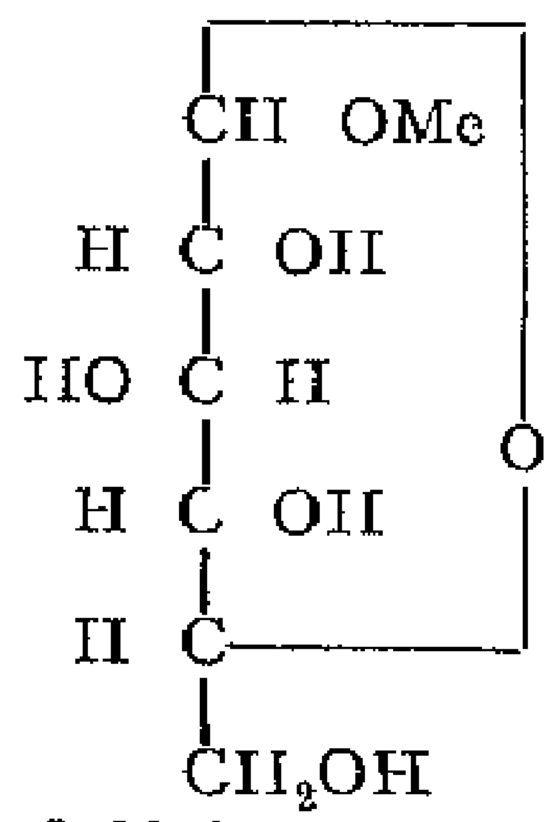
In 1914, Emil Fischer [1] discovered a third form of methyl glucoside, which he described as a γ-form in order to distinguish it from the previously known α- and β-varieties. A year later Irvine isolated a tetramethyl γ-glucose [2] (*i.e.* a γ-glucose having four OH groups replaced by OCH_3) which was extremely reactive; it combined very readily with alcohol and resembled the γ-glucoside in instantly decolorising alkaline permanganate solution. Irvine also showed that Fischer's γ-glucoside was a mixture of two stereoisomeric forms (*cf.* α- and β-methyl glucosides) but found that the corresponding γ-glucose was too labile to be isolated. Owing to its unstable nature the γ-glucose grouping in these compounds was formulated as possessing a different type of ring structure to that present in the α- and β-glucoses and glucosides.

Recent research by Haworth and his co-workers on methylated monosaccharides and lactones of hydroxy acids (see below) has established the fact that the ordinary *pentoses and hexoses normally exist in the 1 : 5- or amylene oxide form* and that the *labile γ-sugars possess a 1 : 4- or butylene oxide ring*. These conclusions are based upon the following lines of argument: (1) a study of the relationships existing between the rotatory powers of the various methylated and unmethylated sugars, (2) the conversion of the monosaccharides into their completely methylated forms, followed by an investigation of the products given by the latter on oxidation, and (3) a study of the rates with which the lactones of the series are hydrolysed to form the open-chain acids. Haworth has shown that among the lactones of the carboxylic acids, the δ-lactones as a class are much more rapidly hydrolysed in water than the γ-lactones.

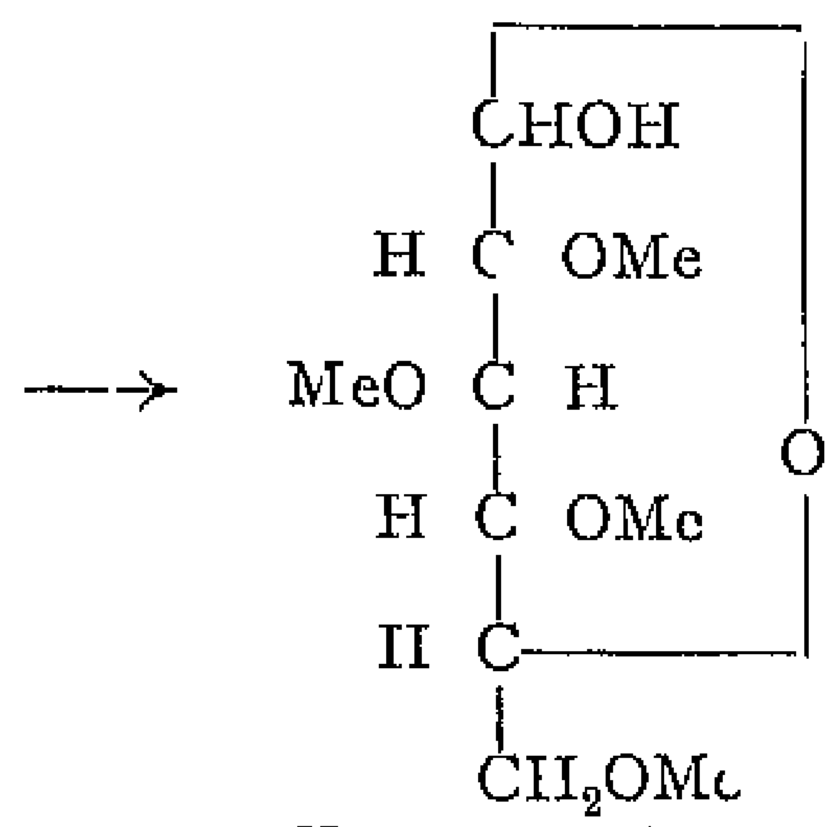
As an example of Haworth's methods we may quote the case of glucose.[3] The α- and β-methylglucosides I (prepared from glucose) were methylated to give the normal crystalline tetramethyl glucose II and this on mild oxidation was converted into the corresponding lactone IV, which from its rate of hydrolysis was characterised as a δ-lactone having the oxygen bridge in the 1 : 5 position. A similar amylene oxide structure may be assumed for the original sugar. Further confirmation of the correctness of these deductions is obtained by the oxidation of the lactone IV to xylotrimethoxyglutaric acid V by means of concentrated nitric acid. Similar methods have been applied to other aldoses and ketoses.

[1] *Ber.*, 1914, 47, 1980. [2] Irvine, Fyfe and Hogg, *J. C. S.*, 1915, 107, 524. [3] For further details see Haworth, *The Constitution of Sugars*; also Charlton, Haworth and Peat, *J. C. S.*, 1926, 89; Haworth, Hirst and Miller, *ibid.*, 1927, 2436; Hirst, *ibid.*, 1926, 350.

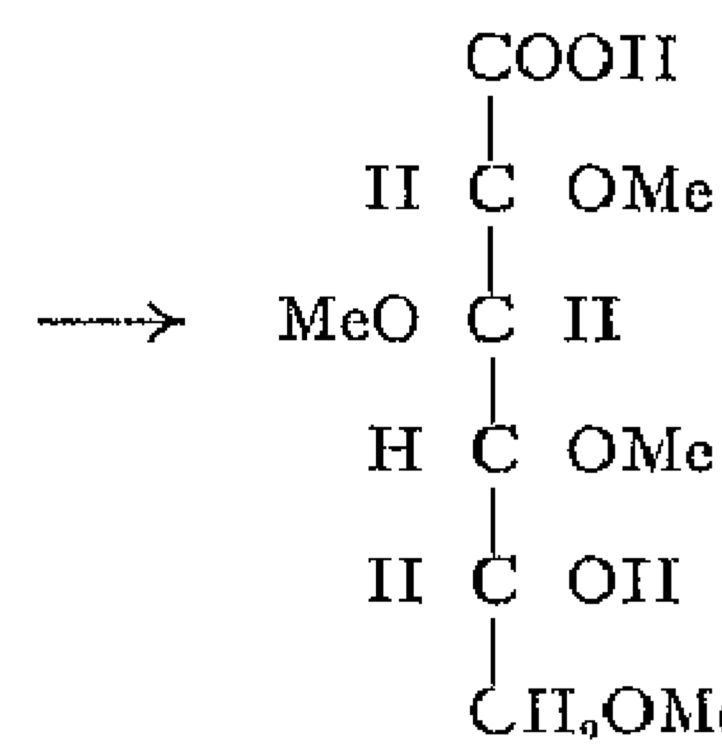
Haworth suggests that the properties of the monosaccharides are most satisfactorily indicated by writing the formulæ as in VI or VII, in which they are represented as being derived from the 6 membered ring compound *pyran* (pyranose structure of sugars) This also illustrates the ease with which the side chain (CH_2OH) in glucose is oxidised to the carboxyl group, yielding glycuronic acid



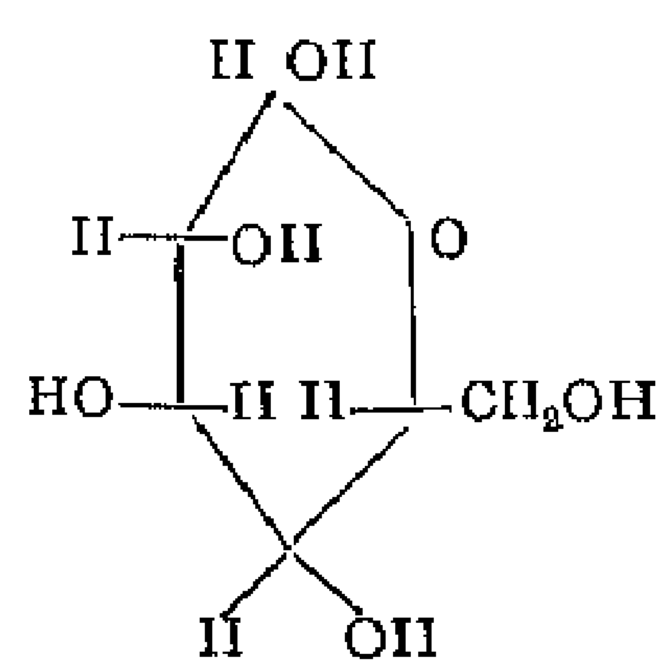
I Methyl glucosides



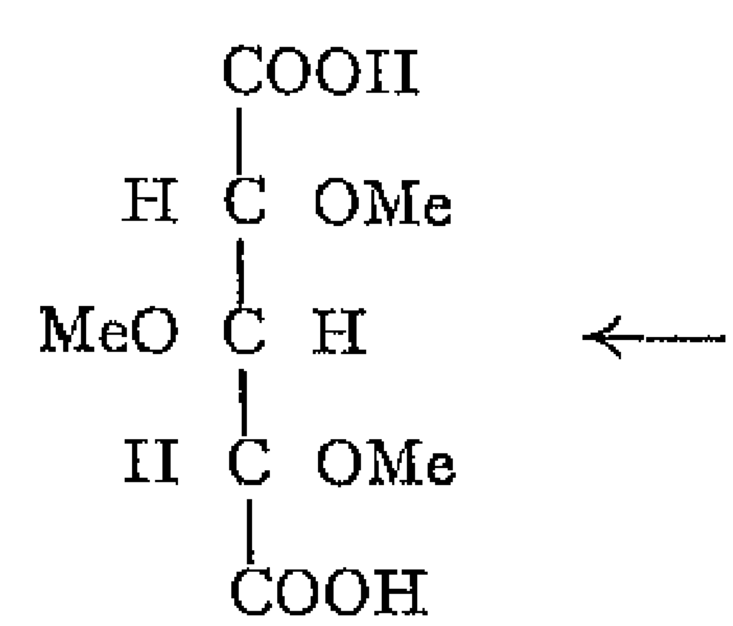
II 2 3 4 6 Tetra-methyl glucose



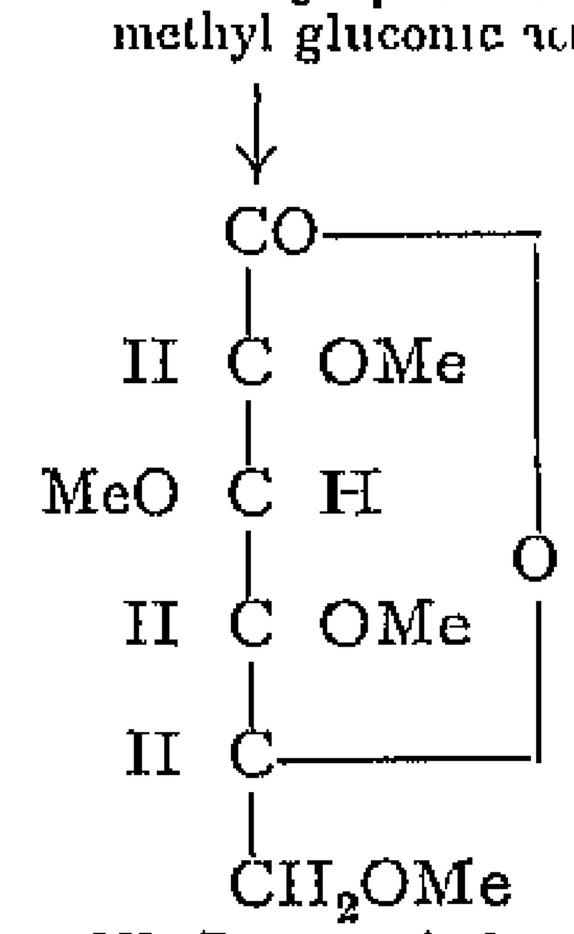
III 2 3 4 6-Tetra-methyl gluconic acid



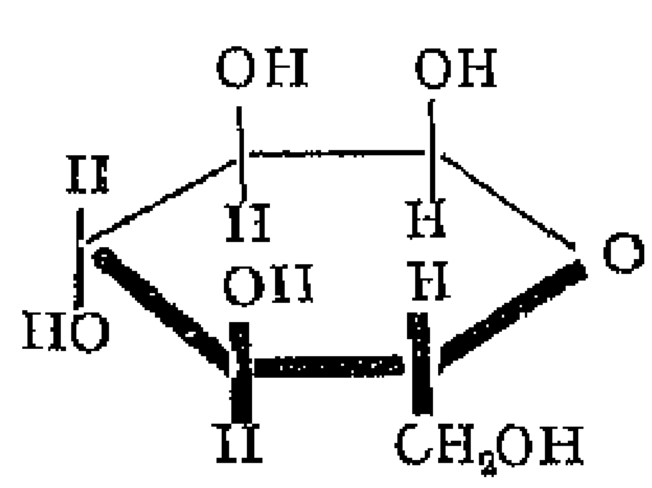
VI *d*-Glucose (α or β)



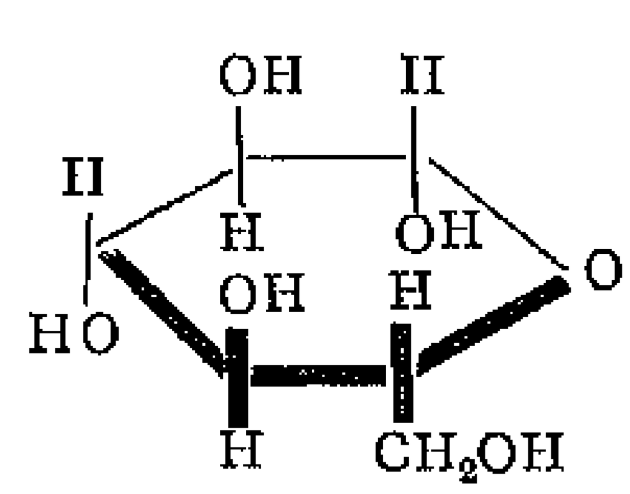
V Xylo trimethoxy-glutaric acid



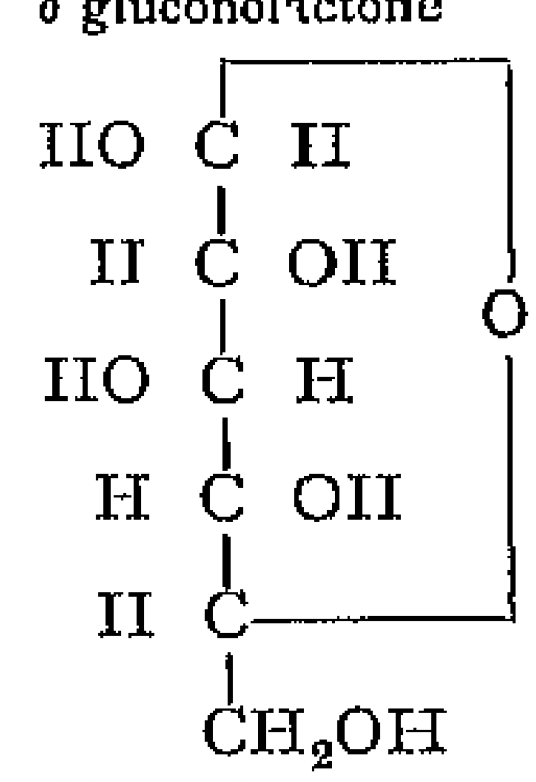
IV Tetramethyl δ gluconolactone



VII α Glucose (in perspective)



VIII β Glucose (in perspective)

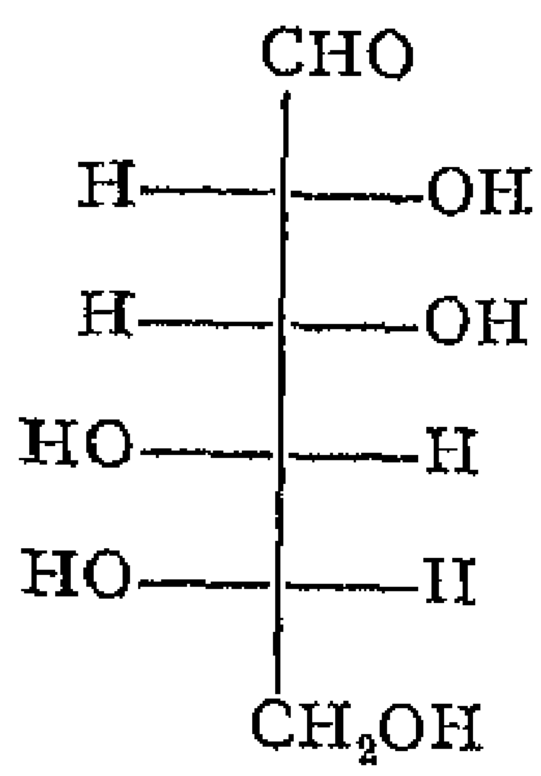


IX β Glucose

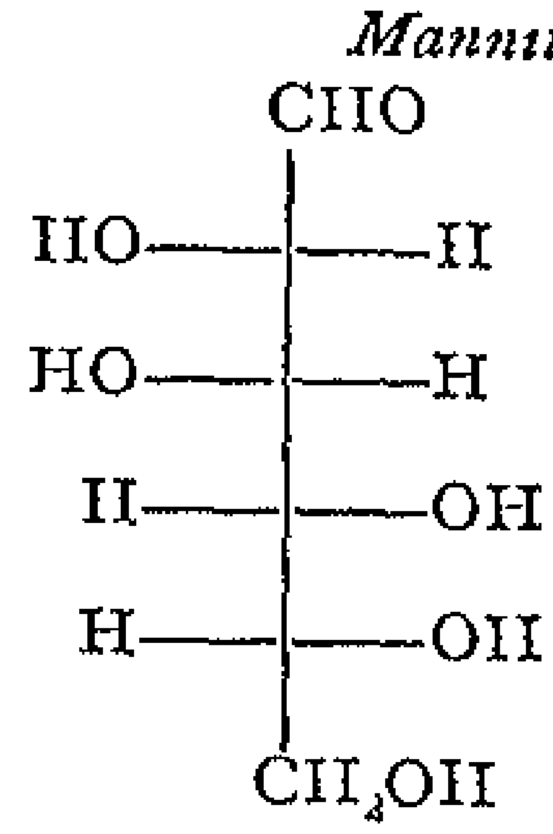
In formulæ such as VI, the usual convention holds as to the disposition of the CHOH groups, a *d* configuration being written with H on the left-hand side When these conventional formulæ are built up in model form, the necessity of bringing the bond joining C_5 to O into the same plane as the other C atoms of the ring is found to cause an apparent displacement of the groups around C_5 (VII and VIII) This change is readily observed on converting the open chain aldehydic model into the ring structure

The Aldohexoses

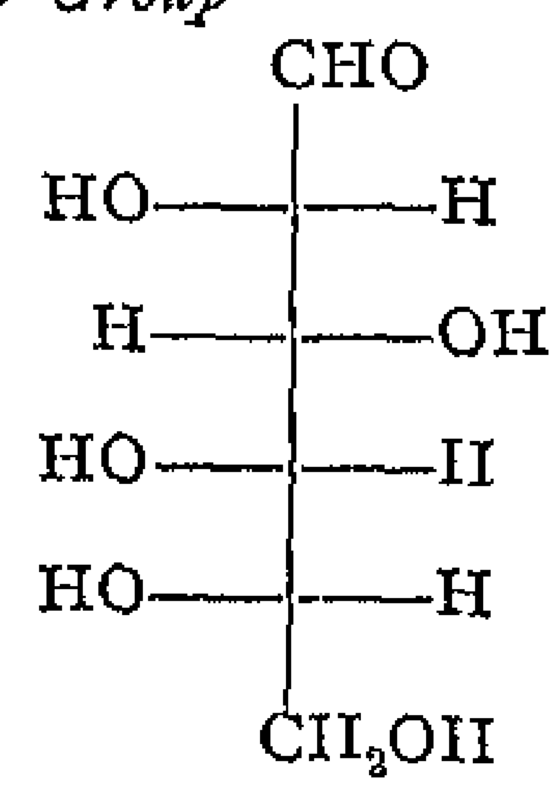
Mannitol Group



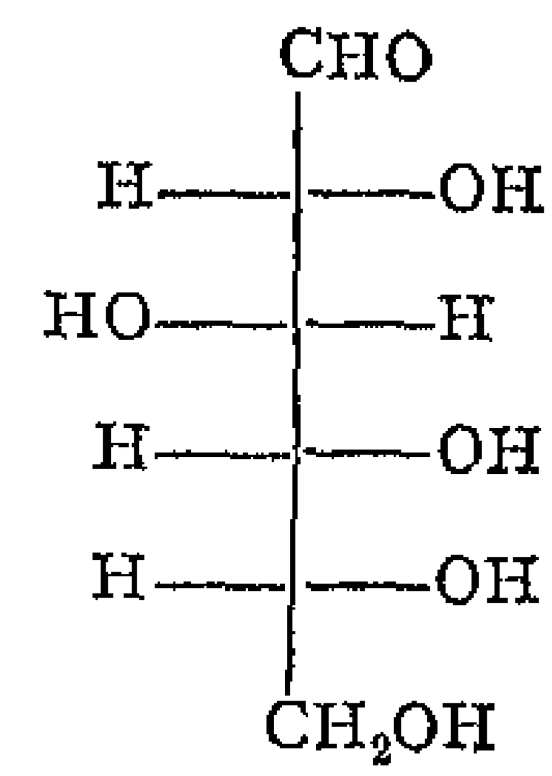
l Mannose



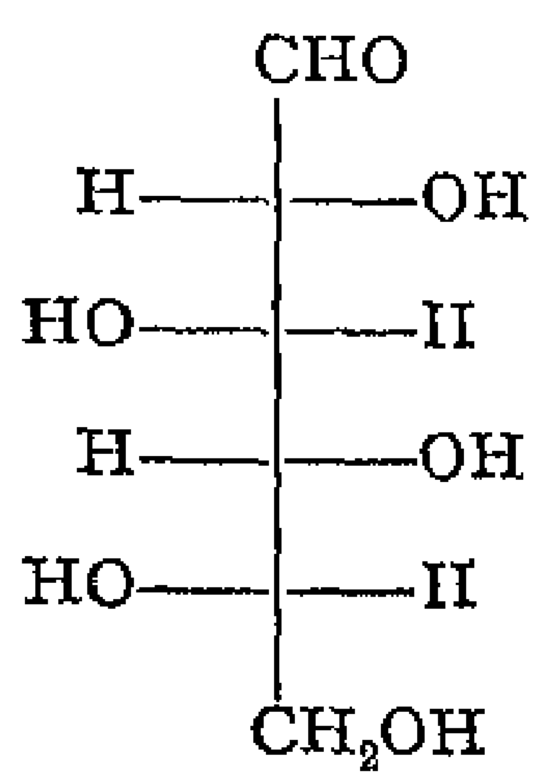
d-Mannose



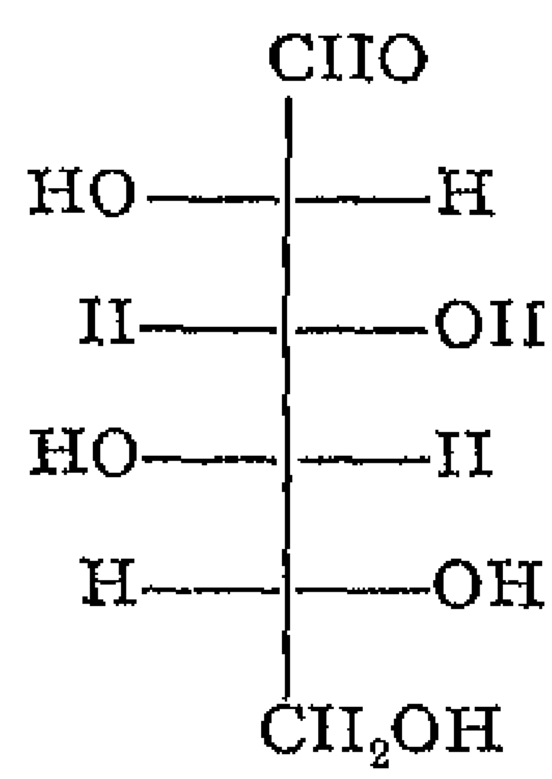
l Glucose



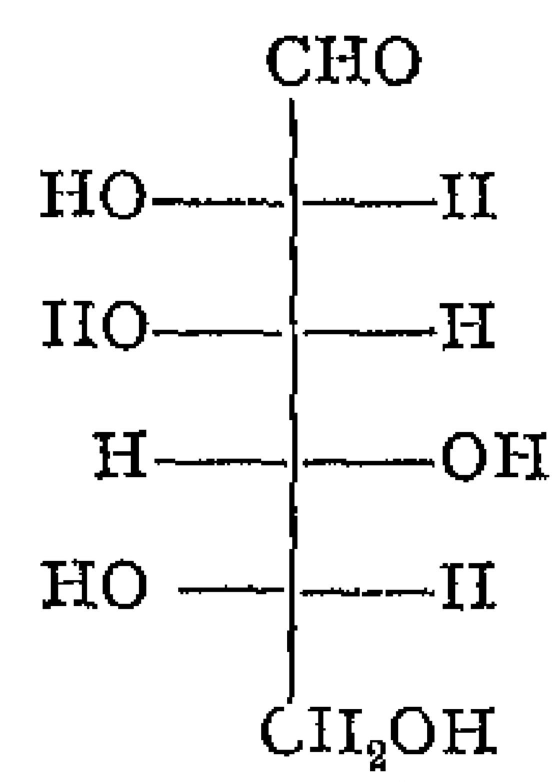
d Glucose



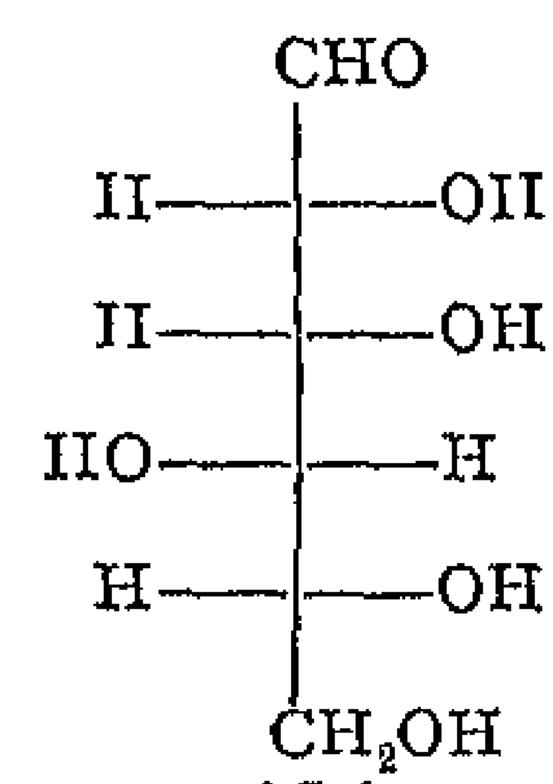
l Idose



d Idose

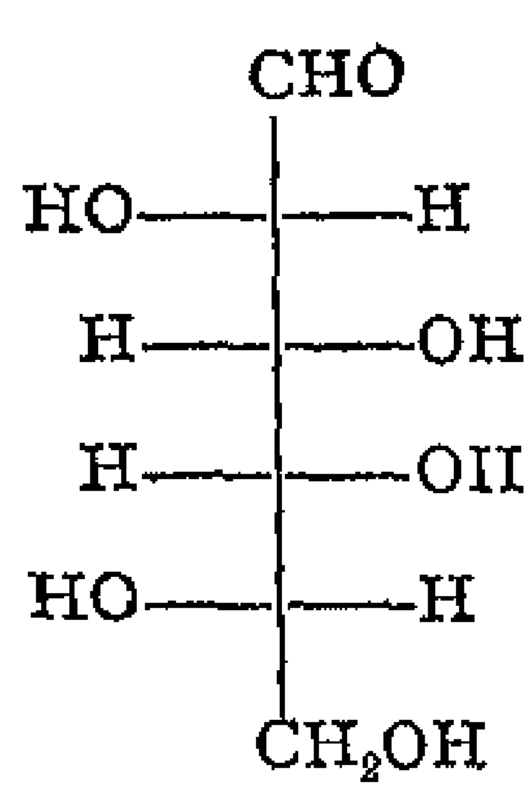


l Gulose

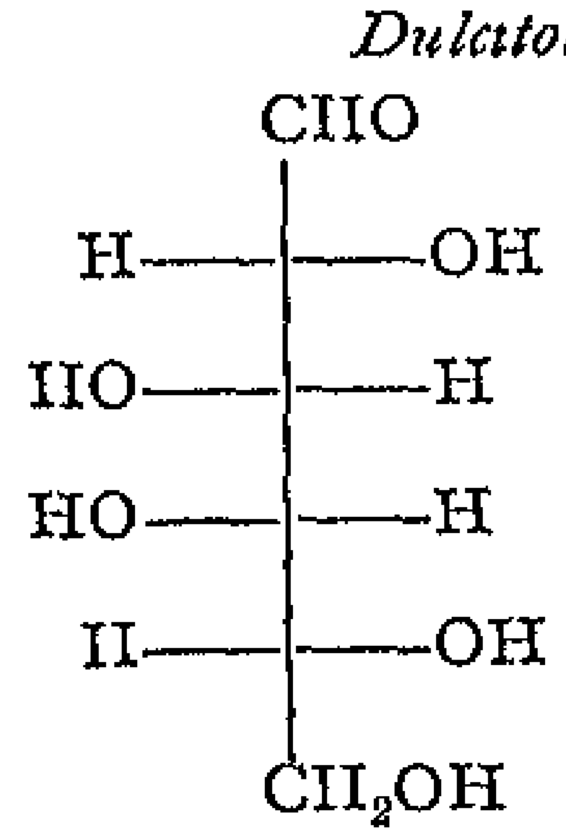


d Gulose

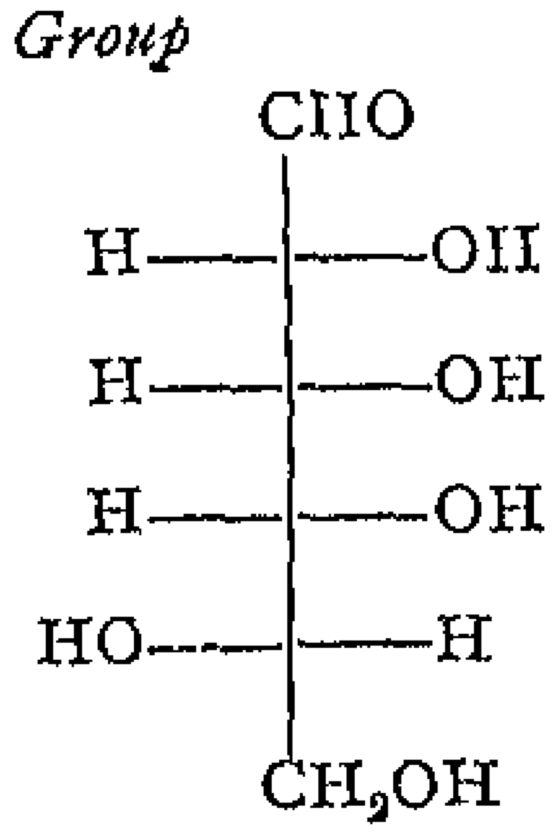
Dulcitol Group



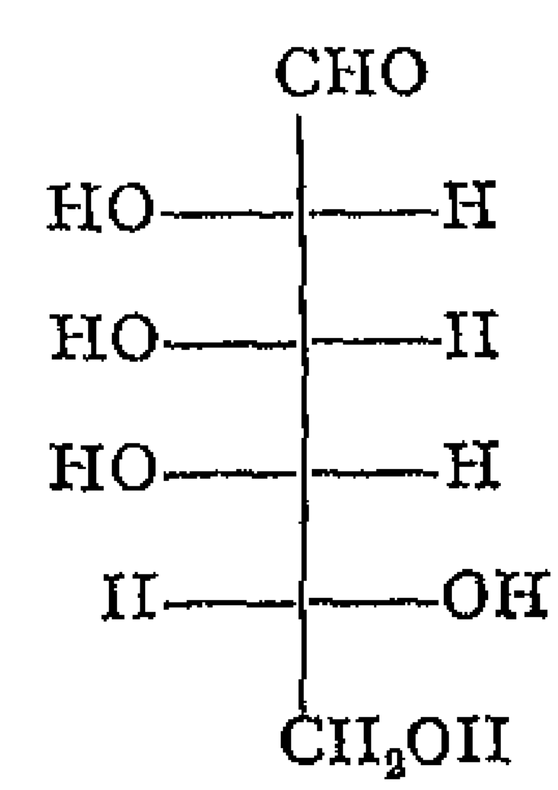
l-Galactose



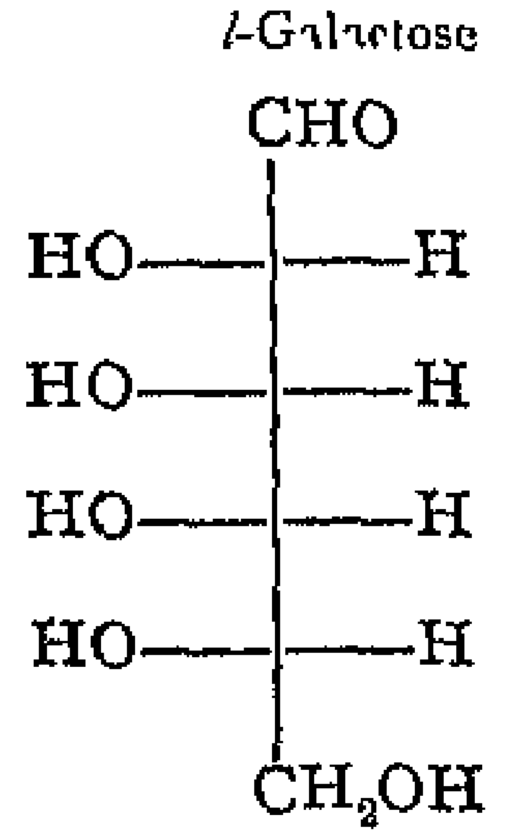
d-Galactose



l Talose



d-Talose



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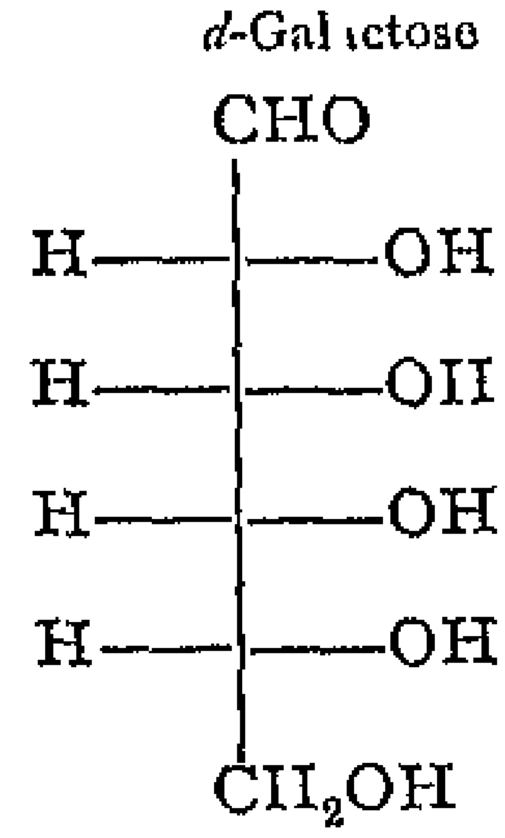
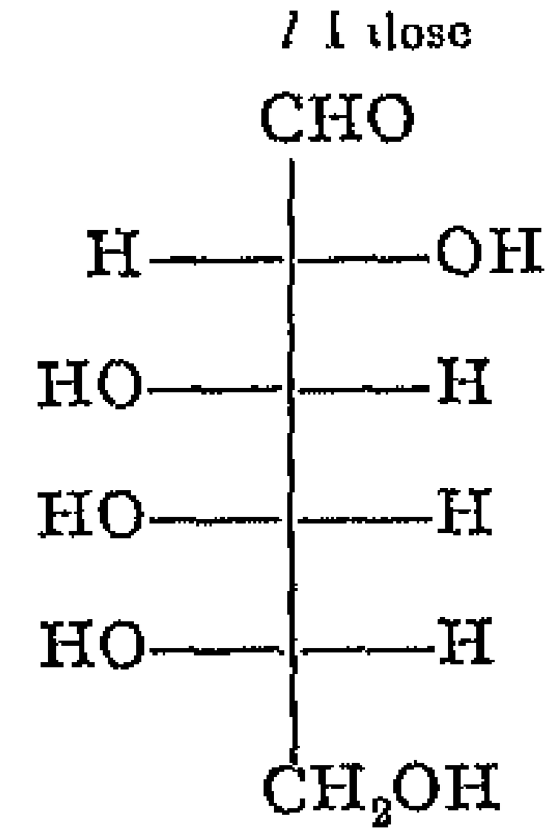


d Allose



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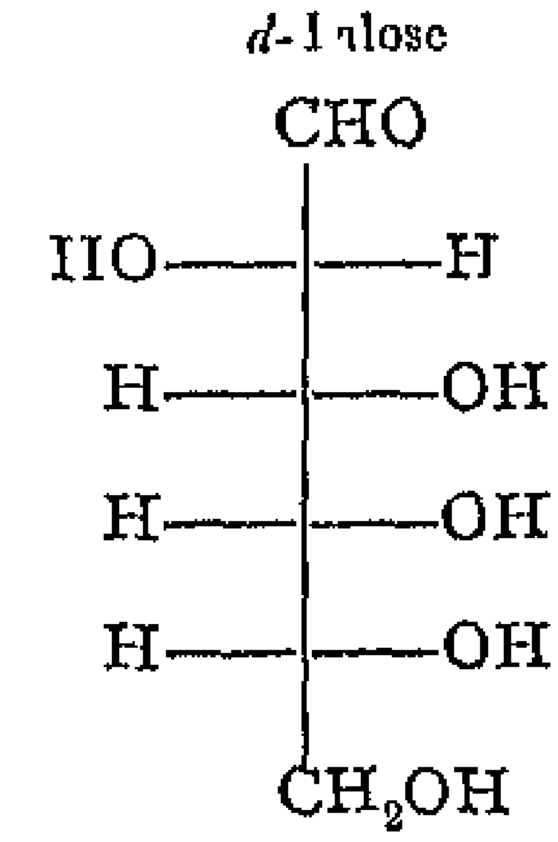


d Altrose

The **ketohexoses** of the structural formula CH_2OH CHOH CHOH CHOH CO CH_2OH, have only three asymmetric carbon atoms, indicating the possible existence of eight optically active forms Like the aldohexoses, the ketohexoses occur normally in a 1 5-oxidic form *d*-Fructose is the most important member of this group

In addition to the general properties of the hexoses quoted on p 289, the following reactions are of interest

When hexoses are treated in alcoholic solution with a little gaseous hydrochloric acid, glucosides or ethers are formed (p 297)

When heated with moderately concentrated hydrochloric acid, hexoses yield *laevulinic acid* (p 264) and in this respect differ from the pentoses By isolating the acid as its silver salt, the reaction can be used as a test for hexoses

A test for ketoses is the evanescent red coloration formed when they are heated with resorcinol and $12\frac{1}{2}$ per cent hydrochloric acid

An outstanding property of certain hexoses is their ability to undergo fermentation As has been shown by E Fischer,[1] this property is intimately connected with the spatial configuration of the sugar

(a) *Aldohexoses*, CH_2OH $(CHOH)_4$ CHO

d-**Glucose**, *grape sugar*, *dextrose*, melts in the anhydrous state at 146°, the hydrated form ($1H_2O$) melting at 86° It is found together with fructose in grapes, figs, and other sweet fruit, and also in honey In small quantities it occurs in certain animal products, *e g* the urine of diabetic patients Glucose and fructose are the only hexoses which occur in the free state

Glucose is also formed by the hydrolysis of the polysaccharides, cane sugar, starch, and cellulose, and is prepared industrially from starch by boiling it with dilute sulphuric acid

The commercial product consists of more or less pure glucose, it is largely used in the manufacture of sweets and in the wine industry

A synthesis of d-*glucose* has been effected by E Fischer in the following manner

Glycerol, on oxidation and subsequent treatment with alkalis, yields α-acrose, identical with *dl* fructose (see p 306) On reduction with sodium amalgam this gives the corresponding alcohol *dl*-mannitol, which on oxidation is converted first into *dl*-mannose, and then into *dl*-mannonic acid By recrystallising the strychnine salts of this acid it may be resolved into its *d*- and *l*-forms When *d*-mannonic acid is heated with pyridine it is partially transformed by epimerisation

[1] Compare p 138 Lack of space forbids any discussion of the interesting researches of Fischer in this connection For details, reference should be made to *Z physiol Ch*, 1898, **26**, 60, see also Armstrong, *The Simple Carbohydrates and the Glucosides*, pp 170 177 (Longmans, Green, 1924)

(p 292) into the stereoisomeric *d*-gluconic acid, the lactone of which on reduction with sodium amalgam finally yields *d*-glucose

According to the conditions of crystallisation, glucose may be obtained anhydrous or combined with one molecule of water Its aqueous solution is dextrorotatory and exhibits mutarotation, a freshly prepared solution rotating the plane of polarisation about twice as strongly as one which has been kept for some time or heated for a few minutes to the boiling-point The final value is $[\alpha]_D = +52\ 5°$

α-Glucose ($[\alpha]_D + 110°$) may be prepared by allowing glucose to crystallise at ordinary temperatures from acetic acid containing a little water Crystallisation at higher temperatures from pure acetic acid[1] yields *β-glucose* ($[\alpha]_D + 17\ 5°$) Ordinary glucose is chiefly the *α*-compound

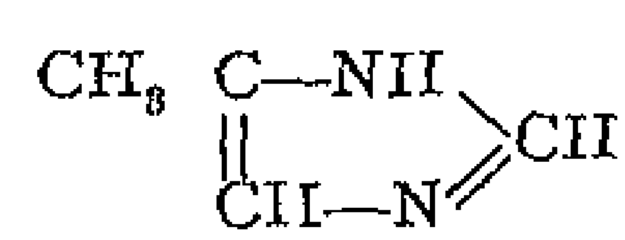
Glucose undergoes the general reactions of aldoses described above On oxidation it first yields *d-gluconic* acid, $CH_2OH(CHOH)_4COOH$, and finally d-*saccharic* acid, $COOH(CHOH)_4COOH$ On reduction it is transformed into the hexahydric alcohol, d-*sorbitol*, $CH_2OH(CHOH)_4CH_2OH$

*Phenyl-*d*-glucosazone* is of importance in the conversion of *d*-glucose into *d*-fructose (see p 290) It is sparingly soluble in water, from which it crystallises in yellow needles, m p 204° to 205°

It has already been mentioned that grape sugar is readily fermented, the main products of the action being alcohol and carbon dioxide

Under the influence of dilute alkalis it suffers a series of changes and decompositions, which lead to the formation of hydroxy acids, such as lactic acid On electrolytic oxidation at a lead anode it breaks up into formaldehyde and a pentose[2]

When treated with ammonia in the form of ammoniacal zinc hydroxide, glucose is converted, even at the ordinary temperature, into methyl-iminazole (methyl glyoxaline)



This reaction has some bearing on the nature of the intermediate products formed during the transformation of grape sugar into lactic acid[3]

***d*-Glucosamine**, *chitosamine*, $CH_2OH\ (CHOH)_3\ CHNH_2\ CHO$, is of special interest, as it stands midway between glucose and the *α*-amino acids, and thus forms a link between the carbohydrates and the proteins It was first prepared from lobster shell by boiling the polysaccharide chitin contained therein with hydrochloric acid[4]

[1] Hudson and Dale, *J A C S*, 1917, 39, 320 [2] W Löb and Pulvermacher, *Biochem Zeitsch*, 1909, 17, 343 [3] Windaus and Knoop, *Ber*, 1905, 38, 1166, 1906, 39, 3886, 1907, 40, 799 [4] The complex compound chitin appears to be closely related to N acetyl glucosamine T R Offer, *Biochem Zeitschr*, 1907, 7, 117 K H Meyer, *Zeit für ang Chem*, 1928, 41, 941, *Ber*, 1928, 61, 1936

Recently it has been found that glucosamine and other hexosamines are formed from mucins, the constituents of animal mucus, and from other proteins by hydrolysis with acids The relationship of glucosamine to grape sugar is shown by its conversion into phenylglucosazone on treatment with phenyl-hydrazine

d-Glucosamine has been synthesised by Fischer and Leuchs[1] in the following manner *d* arabinose, by treatment with ammonia, was converted into *d*-arabinosimine, which with hydrogen cyanide gave *d*-glucosaminic acid, $CH_2OH\ (CHOH)_3\ CH(NH_2)\ COOH$ The lactone of this acid was then reduced to *d*-glucosamine by means of sodium amalgam

d-*Glycuronic acid*, $HOOC\ (CHOH)_4\ CHO$, is obtained by the reduction of saccharic acid, $HOOC\ (CHOH)_4\ COOH$ It occurs in urine, either united with phenols in compounds of an ether type or with aromatic carboxy acids in the form of esters In this way the phenols resulting, for example, from intestinal putrefaction are rendered harmless to the body This protective function of glycuronic acid is also exerted by sulphuric acid and glycocoll Glycuronic acid does not crystallise, and in this respect differs from its lactone, glycurone

l **Glucose** is formed in the same manner as *d* glucose by reducing the lactone of *l* gluconic acid Similarly *dl* **glucose** can be obtained from *dl* gluconic acid *l*-Glucose forms crystals of melting point 141°, but *dl* glucose is a syrup

d-**Mannose** is produced by careful oxidation of the hexahydric alcohol mannitol, which is present in various plants, or by boiling the polysaccharide seminine,[2] occurring in the shell of the ivory nut, with dilute sulphuric acid Synthetically, it is obtained by reducing *d*-mannonic acid with sodium amalgam It is a white hygroscopic compound of lower rotatory power than *d*-glucose, from which it differs only in the relative arrangement of the groups attached to the carbon atom adjacent to the aldehyde group (see p 301) From this it follows that *d*-mannose and *d*-glucose yield the same osazone

Oxidation converts *d*-mannose first into *d*-mannonic acid, $CH_2OH(CHOH)_4\ COOH$, and then into *d*-manno-saccharic acid, $COOH\ (CHOH)_4\ COOH$ It can be fermented with yeast

The conversion of *d*-mannose into *d*-glucose may be effected through the intermediate formation of *d*-mannonic acid

l **Mannose** has been prepared from *l* arabinose by the cyanhydrin synthesis and is laevorotatory It unites with *d* mannose to give **inactive mannose**, which is also formed by oxidation of the *dl* mannitol obtained by reducing *dl* fructose

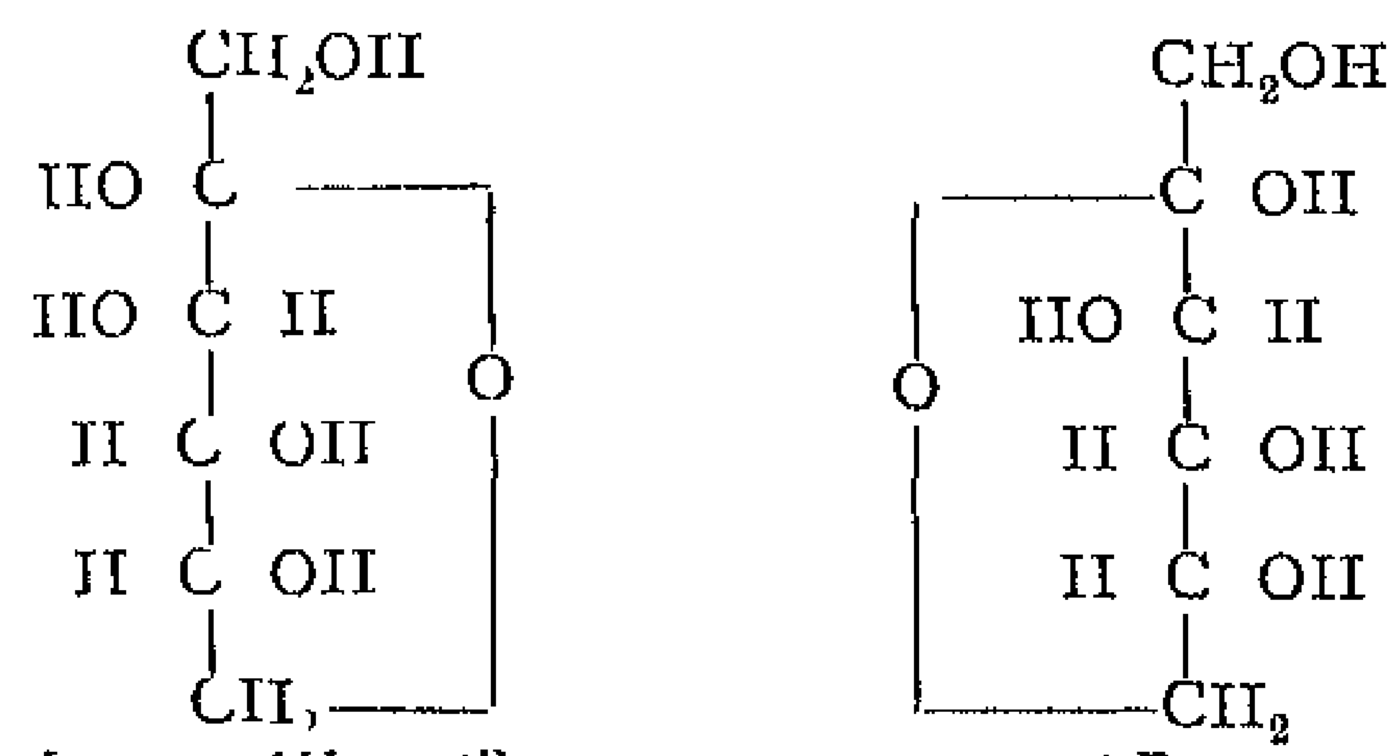
d-**Galactose** occurs in the ivy[3] It is formed together with *d* glucose by the hydrolysis of milk sugar, and also of *galactitol*, $C_6H_{13}O_7$, a substance present in the yellow lupin It melts at 168°, is dextrorotatory, exhibits mutarotation and may be fermented On

[1] *Ber*, 1903, 36, 24 [2] P M Horton, *J Indus and Eng Chem*, 1921, 13, 1040 [3] v Lippmann, *Ber*, 1910, 43, 3611

reduction it yields i-*dulcitol* (p 246), and on oxidation gives first *galactonic acid*, $CH_2OH\,(CHOH)_4\,COOH$, and then *mucic acid*, $COOH\,(CHOH)_4\,COOH$

(b) *Ketohexoses*, $CH_2OH\,(CHOH)_3\,CO\,CH_2OH$

d(–)**Fructose**, *fruit sugar*, *laevulose*, m p 95°, is found with *d*-glucose in honey and the juice of sweet fruits The hydrolysis of cane sugar leads to the production of equimolecular amounts of *d*-fructose and *d*-glucose On the other hand, inulin, a polysaccharide occurring in the roots of the dahlia, chicory and many *Compositæ*, yields *d*-fructose alone From the latter sources it is prepared industrially



α Fructose (*Haworth*) β Fructose

Fructose yields the same osazone as glucose (compare the configurational formulæ) and the *conversion of glucose into fructose* by way of the osazone has already been described on p 291 In consequence of its spatial relationship to *d*-glucose, fruit sugar is known as *d*-fructose, although it has a laevorotation of $[\alpha]_D = -92°$

Fructose is less soluble in water than glucose, and is readily fermented, when it gives the same products as grape sugar On reduction it is converted into a mixture of *d*-mannitol and *d*-sorbitol On oxidation it breaks up into *d*-erythronic acid, $CH_2OH\,(CHOH)_2\,COOH$, and glycollic acid, $CH_2OH\,COOH$

Interconversion of d-*Glucose*, d-*Fructose*, *and* d-*Mannose*[1]

As was first shown by Lobry de Bruyn, any one of the above three hexoses, under the influence of hydroxyl ions (very dilute alkalis or alkaline earths, sodium acetate, ammonia, etc), is converted into a mixture of all three sugars in equilibrium with one another, as indicated in the following scheme

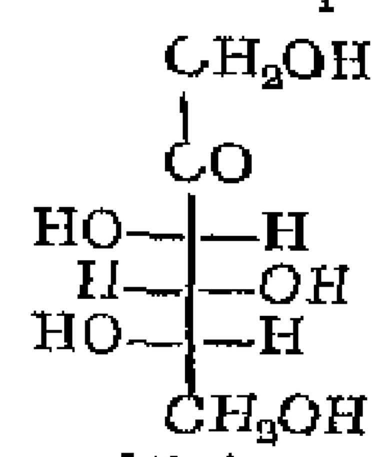
$$\text{Glucose} \rightleftharpoons \text{Fructose} \rightleftharpoons \text{Mannose}$$

d-Fructose appears to be formed as an intermediate in the above changes This is strongly supported by the fact that mannose, of $[\alpha]_D = +14°$, yields with dilute alkalis a strongly laevorotatory

[1] Lobry de Bruyn and A van Ekenstein, *Ber*, 1895, 28, 3078

mixture (owing to the formation of fructose), the rotation subsequently swinging back towards zero as the proportion of glucose increases

l **Fructose** is produced by the fermentation of racemic fructose It is the optical enantiomorph of the laevorotatory *d* fructose, and is therefore dextrorotatory



l Sorbose

dl **Fructose**, or *a* **Acrose**, is the resolvable inactive form produced synthetically from glycerose or formaldehyde, and has played a most important part in the synthesis of sugars

l **Sorbose**, *sorbinose*, m p 154°, is a ketose obtained from the juice of mountain ash berries These contain the alcohol sorbitol, which is converted into sorbose by the action of an oxidising organism, *Bacterium xylinum* It is not fermented by yeast

Glucosides [1]

In close relationship to the monosaccharides are the glucosides, which are found very widely distributed in the vegetable kingdom They may be considered as derivatives of the ether type formed by combination of a sugar (commonly glucose) with one or more other substances Well known representatives of this class are *amygdalin*, a constituent of bitter almonds, and *salicin*, which was used as a febrifuge by the older school of medicine Under the influence of enzymes, or on being heated with dilute acids or alkalis, the glucosides break up into a hexose and the remaining constituents

Glucosides of the simplest type have been synthesised by E Fischer,[2] by bringing a sugar, *e g* glucose, into reaction with an alcohol in the presence of hydrochloric acid

$$C_6H_{12}O_6 + CH_3OH = C_6H_{11}O_5 \cdot OCH_3 + H_2O$$

Another compound of similar structure, which has recently come into use in the synthesis of glucosides and other sugar derivatives, is *aceto bromo glucose*,[3] prepared from penta acetyl glucose by treatment with hydrobromic acid

$$CH_2(OAc) \cdot \underbrace{CH \cdot [CH(OAc)]_3 \cdot CHBr}_{O}$$

As is shown by the inactivity of these compounds towards phenyl hydrazine, they no longer contain a free aldehyde group The latter must therefore be united to the alcohol in the same manner as in the acetals (see p 169) For the isomerism of *a* and *β* glucosides and a means of distinguishing between these two forms by enzyme action, see p 297 *et seq*

A detailed investigation of the simpler artificial glucosides led Fischer to the discovery that there was no fundamental difference between the glucosides and the polysaccharides The latter are glucosides of the monosaccharides themselves

Linamarin, the glucoside of acetone cyanhydrin, $C_6H_{11}O_5 \cdot O \cdot C(CH_3)_2 \cdot CN$, was first isolated from the seeds and embryo of flax It forms colourless needles, m p 134°, possessing a fresh bitter taste On hydrolysis with dilute acids it decomposes into glucose, hydrogen cyanide, and acetone It has also been prepared synthetically [4]

4 Heptoses, Octoses and Nonoses

By means of the cyanhydrin synthesis described on p 291, it is possible to convert an aldohexose by successive stages into the corresponding heptose, octose and nonose Of these it need only be mentioned that the heptoses and octoses are not fermentable, whereas *d* manno nonose ferments with yeast

[1] See E F Armstrong, *The Simple Carbohydrates and the Glucosides* (Longmans, Green 1924) [2] E Fischer, *Ber*, 1893, 26, 2400, 1895, 28, 1145, 1909, 42, 1465 [3] Compare *Ber*, 1920, 53, 440, 2150, 1921, 54, 499, 1922, 55, 929 [4] *Ber*, 1919, 52, 854

II.—DISACCHARIDES, $C_{12}H_{22}O_{11}$

Unlike the higher polysaccharides, the di- and trisaccharides still retain the sweetness of taste characteristic of monosaccharides.

Until recently the only disaccharides known were derived from the hexoses, $C_6H_{12}O_6$, and therefore possessed the formula $C_{12}H_{22}O_{11}$. On hydrolysis these take up water and are decomposed into two hexose molecules, $C_{12}H_{22}O_{11} + H_2O = 2C_6H_{12}O_6$. This change may be effected by boiling with dilute acids, or by the action of enzymes such as diastase, emulsin and invertase. All disaccharides yield glucose as one of the hydrolytic products, the other may also be glucose (as in the case of maltose), fructose (from cane sugar), or galactose (from milk sugar).

Disaccharides have now been found in plants which give on hydrolysis 1 mol. hexose and 1 mol. pentose, *e.g.* *vicianose* (*Bertrand*) an arabinosido glucose, and *primverose*, a xylosido-glucose. Both of these disaccharides have been synthesised by Helferich.[1]

The ease with which disaccharides are hydrolysed supports the view that they are ethereal anhydrides of hexoses, the link joining the two hexose molecules being supplied by the oxygen of an alcoholic, aldehydic or ketonic group. If union occurs in such a way that the reducing group of one of the hexose constituents is left intact, then the disaccharides so formed (*e.g.*, lactose and maltose) will still exhibit the reactions of aldoses. They will reduce Fehling's solution and give osazones with phenyl-hydrazine. On the other hand, cane sugar shows none of these reactions, and in it the reducing groups of both glucose and fructose appear to be bound.

Synthetic methods have only met with success within the last few years, a number of the natural disaccharides having been synthesised by processes which have been based upon the constitutions deduced by analytical methods of investigation.

In determining the constitution of di- and polysaccharides the chief difficulty lies in deciding the exact position of the oxygen linkings taking part in anhydride formation, and the particular stereoisomeric form of the monosaccharides present. Some information on these points is afforded by a study of enzyme action.

In recent years this problem has been attacked systematically on lines developed by Purdie, Irvine, Haworth and others. The method adopted involves, in the first instance, the preparation of a large number of partially or completely methylated aldoses and ketoses.[2] The polysaccharide under investigation is then fully methylated[3] and submitted

[1] B. Helferich and co-workers, *Ann.*, 1927, 455, 168; 1928, 465, 166. [2] Irvine and co-workers, *J. C. S.*, 1913, 103, 564, 575; 1916, 109, 1305; 1922, 121, 2696. For a detailed description of the methods employed, see "Some Constitutional Problems of Carbohydrate Chemistry," Irvine, *J. C. S.*, 1923, 123, 898. [3] For the use of methyl sulphate in this connection, see W. N. Haworth, *J. C. S.*, 1915, 107, 8.

to careful hydrolysis or other chemical change. From an examination of the simpler methylated derivatives so obtained it has in a number of cases been possible to determine the structure of the parent compound.[1]

Cane Sugar, *sucrose, saccharose,* m.p. 160°, occurs in the juice of the sugar cane, sugar beet, sugar maple, maize, and many other plants. The first two sources are utilised in the preparation of sugar on the large scale.

Technical Preparation of Sugar from Beets.—The beets are sliced into thin sections by mechanical means, and the sugar is extracted by a *diffusion process* involving systematic treatment with water.[2] The water is first admitted to a "diffuser" containing the almost completely extracted roots, and after remaining there for a few minutes is transferred to the next in the series, finally coming into contact with fresh roots. The completely extracted roots are expressed and utilised as fodder, after being dried to keep them in good condition.

The subsequent *processes for purifying the juice* have as their aim the removal of the majority of other organic substances present, which would otherwise hinder the crystallisation of the sugar. For this purpose the extract is treated at a moderate temperature with milk of lime, by which means oxalic acid, citric acid, and phosphates are precipitated, other acids are neutralised or, like asparagine, decomposed, and most of the protein and colouring matter is thrown out of solution. The necessity of using an excess of lime leads to the formation of insoluble calcium sucrate; this is decomposed by passing in carbon dioxide, when calcium is precipitated as calcium carbonate. Sulphur dioxide is frequently used in place of carbon dioxide, and yields an extract of better colour.

In order to avoid decomposition the *evaporation of the purified extract* is conducted in vacuum pans, and is continued until a concentration is reached at which crystallisation sets in. Finally the masses of crystals are broken up and the mother liquor removed by centrifuging. The moist crystals remaining in the centrifuge constitute the *raw sugar* of commerce, and the dark brown fluid which is run off is known as *molasses*.

Raw sugar is refined by bringing it into solution, treating with milk of lime, and filtering through "activated" charcoal. After several repetitions of this process the liquid is concentrated in vacuum pans until crystallisation sets in. The refined sugar so obtained contains 99.9 per cent saccharose.

[1] Irvine, Steel and Shannon, *J. C. S.*, 1922, 121, 1060; Haworth and Leitch, *J. C. S.*, 1918, 113, 188; 1919, 115, 809. [2] Methods are also under investigation by which the sliced beets are dried and stored. This allows the extraction process to be operated throughout the year, independently of the seasonal supply of raw material.

Recovery of Molasses —Molasses contains about 20 per cent water and 50 per cent sugar The latter, however, is only in part recoverable by further concentration of the molasses, as it is held in solution by the presence of impurities It is therefore necessary to separate the sugar from the residual matter by special treatment, for which purpose a large number of processes are available

(*a*) *The Osmotic Process* consists in dialysing the molasses through parchment paper, when inorganic salts are the first to diffuse out of the mixture, followed by organic salts, salts and sugar, and finally sugar alone Albuminous substances which had previously hindered crystallisation, being colloidal in nature, are unable to pass through the membrane The diffused liquid is worked up for sugar by evaporation *in vacuo*, and the albuminous residue, which still contains a certain amount of sugar, is used as a fertiliser

(*b*) Separation by means of *strontium* or *calcium sucrates* This process depends on the property which sugar possesses of giving insoluble or sparingly soluble sucrates with lime or strontium hydroxide, *e g tricalcium sucrate*, $C_{12}H_{22}O_{11}$, 3CaO, *distrontium sucrate*, $C_{12}H_{22}O_{11}$, 2SrO When the diluted molasses is treated with either of the above hydroxides a precipitate of the corresponding sucrate is thrown out of solution Inorganic and organic impurities in the molasses remain dissolved and are removed in a filter press After washing the sucrates with a little water or aqueous alcohol they are decomposed with carbon dioxide, and the sugar solution so obtained is evaporated as before in vacuum pans

Properties of Cane Sugar —Cane sugar crystallises in clear monoclinic prisms, which are very sparingly soluble in alcohol, but dissolve easily in water to give a solution rotating the plane of polarisation to the right Cane sugar melts at 160° and on cooling solidifies to a vitreous mass (*barley sugar*), which gradually reverts to the crystalline state On stronger heating it forms a brown product known as *caramel*, a mixture of decomposition products of sugar used for tinting liqueurs and confectionery As has already been mentioned above, it forms sucrates with bases When warmed with dilute acids it is rapidly hydrolysed to a mixture of glucose and fructose Glucose resembles cane sugar in being a dextrorotatory compound, but fructose is so strongly laevorotatory that the equimolecular mixture of glucose and fructose obtained by hydrolysis rotates the plane of polarisation to the left For this reason the above process is known as the *inversion of cane sugar*, and the mixture of *d*-glucose and *d*-fructose so obtained as *invert sugar* The latter usually forms a syrup, which is sweeter than cane sugar and is used as a substitute for honey, for improving wine musts, and in the preparation of champagne, liqueurs and fruit preserves

Cane sugar no longer gives the reactions of the monosaccharides,

e.g. it forms no osazone and does not reduce Fehling's solution. On heating with acetic anhydride it yields an octa-acetyl derivative. Working from these data E. Fischer suggested the following formula for cane sugar:

$$\mathrm{CH_2OH\cdot CHOH\cdot \overbrace{CH\cdot(CHOH)_2\cdot CH}^{O}\!-\!O\!-\!\overbrace{\underset{CH_2\cdot OH}{\underset{|}{C}}\cdot(CHOH)_2\cdot CH}^{O}\cdot CH_2OH}$$

Glucose residue Fructose residue

Recent work on the oxidation of octamethyl-sucrose and its hydrolysis products,[1] however, points to the glucose residue possessing an amylene oxide structure in place of the butylene oxide structure given above, leading to the formula

$$\mathrm{CH_2OH\cdot \overbrace{CH\cdot(CHOH)_3\cdot CH}^{O}\!-\!O\!-\!\overbrace{\underset{CH_2OH}{\underset{|}{C}}\cdot(CHOH)_2\cdot CH}^{O}\cdot CH_2OH}$$

Glucose residue Fructose residue

It may be noted that the fructose residue in this case possesses the labile 1 : 4- and not the normal 1 : 5-oxidic ring, and that the aldehydic and ketonic groups of glucose and fructose have both been masked by anhydride formation.

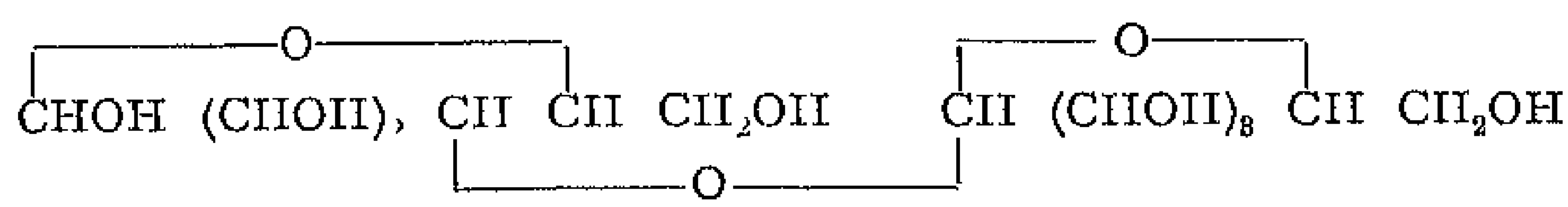
The above formula for cane sugar has been confirmed by the synthesis of A. Pictet and Vogel.[2] Among the acetylation products of fructose these authors found a very small proportion of a liquid dextrorotatory tetra-acetyl fructose. This was separated from the normal crystalline laevorotatory variety, which is the main product of the reaction, and condensed with normal tetra-acetyl glucose in chloroform solution in the presence of phosphoric anhydride. The resulting octa-acetyl sucrose gave sucrose itself after removal of the acetyl residues.

Milk Sugar, *lactose*, *lactobiose*, is found almost exclusively in the milk of mammals. It is prepared industrially from whey, obtained as a by-product in the manufacture of cheese from milk. The whey is evaporated in vacuum pans until crystallisation sets in, and the crude milk sugar so obtained is purified by recrystallisation from water with the addition of animal charcoal.

It forms hard rhombic crystals containing one molecule of water, which become anhydrous at 140° and then melt with decomposition at 205°. It is dextrorotatory and undergoes mutarotation. On hydrolysis it decomposes into *d*-galactose and *d*-glucose. Lactose forms an osazone and reduces Fehling's solution. The carbonyl group present in the molecule is that corresponding to *d*-glucose, since lactose, on oxidation with bromine water, yields lactobionic acid,

[1] Avery, Haworth and Hirst, *J. C. S.*, 1927, 2308; Haworth, Hirst and Nicholson, *ibid.*, 1513; Haworth, Hirst and Learner, *ibid.*, 2432. [2] *Helv. Chim. Acta*, 1928, 11, 436.

which on hydrolysis breaks up into *d*-galactose and *d*-gluconic acid These facts, together with the results of a recent examination of the behaviour of the completely methylated sugar on hydrolysis,[1] point to the following formula for lactose



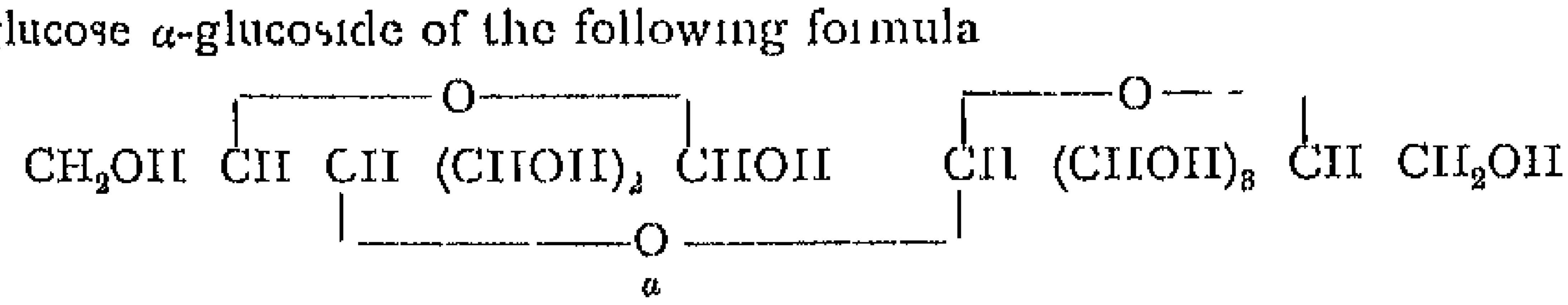
Glucose residue Galactose residue

Lactose is not as sweet as cane sugar It is used in medicine, in the silvering of mirrors, and is frequently added to milk intended for infant consumption It is not easily fermented with yeast but readily undergoes lactic acid fermentation Alcoholic fermentation may also be induced by means of kefir grains *Koumiss* is a Russian beverage made in a similar way by fermenting mare's milk

Malt Sugar, *maltose*, maltobiose, is produced, as already mentioned on p 137, by the action of diastase on starch, and is an important intermediate product in the preparation of alcohol and alcoholic liquors

In the *technical preparation of maltose* starch is mixed to a paste with a sufficient quantity of water and the addition of 1 to 3 per cent of green malt (see p 137), the temperature of the fluid being kept below 70° It is then cooled to 55°, a further 4 to 7 per cent of green malt added and the mixture maintained at this temperature till all the starch is decomposed The solution of malt sugar is boiled in order to coagulate dissolved protein, and insoluble matter is filtered off to be used as cattle food The concentrated liquid may be used to prepare crystalline maltose, or may be placed on the market as *malt syrup* or *malt extract*

Maltose crystallises from water in small needles (1 mol H_2O), which melt at 100° when rapidly heated It is strongly dextro-rotatory, and on hydrolysis with dilute acids yields *d*-glucose alone It gives the same reactions as the monosaccharides, reducing Fehling's solution and forming an osazone In these respects maltose resembles lactose It can be oxidised to malto-bionic acid, which contains the same number of carbon atoms and is monobasic The latter on hydrolysis yields *d*-gluconic acid Hence it may be concluded that maltose is composed of two molecules of glucose united in such a way that the aldehyde group of the one remains intact, while that of the other has entered into anhydride formation[2] It is represented as a glucose α-glucoside of the following formula



[1] Haworth, Leach and Long, *J C S*, 1927, 3150

[2] For the structure of maltose, see Haworth and Peat, *J C S*, 1926, 3094

Maltose has been synthesised[1] by heating a mixture of α- and β-glucoses in a vacuum at 160°

Trisaccharides, $C_{18}H_{32}O_{16}$

Few examples of this group of polysaccharides have been discovered, the best known representative being raffinose, *melitose* or *melitriose*, which forms the chief constituent of Australian manna It also occurs in beetroot, and is consequently found in beet molasses Raffinose crystallises in fine needles with five molecules of water of crystallisation, which are driven off at 120° On hydrolysis it takes up two molecules of water, yielding an equimolecular mixture of *d* fructose, *d* glucose, and galactose Raffinose shows none of the reactions of the monosaccharides, and we must therefore assume that it is built up from the above three sugars in such a manner that all three carbonyl groups are modified by intramolecular linkage

III —HIGHER POLYSACCHARIDES $(C_6H_{10}O_5)_n$

As has already been stated on p 287, the formula of these compounds is usually expressed as $(C_6H_{10}O_5)_n$ It was shown by Kiliani[2] that this is not a correct representation of their composition Properly speaking, the formula is $(C_6H_{10}O_5)_n$, H_2O or $C_{6n}H_{(10n+2)}O_{5n+1}$, in which n is unknown, although certainly not small The majority of the polysaccharides are amorphous, tasteless compounds, some of which are insoluble in water When hydrolysed by boiling with dilute acids, or by treatment with enzymes, they are all converted into monosaccharides, which may be either hexoses or pentoses The polysaccharides are therefore considered to be built up from hexoses and pentoses by means of oxygen linkings, in the same manner as the di- and trisaccharides The presence of hydroxyl groups is shown with certainty by their property of forming acetyl derivatives and nitric esters

Polysaccharides are found widely distributed in the plant and animal kingdoms But whereas in the animal organism only two polysaccharides, *glycogen* and *cellulose*,[3] have so far been discovered, the number occurring in the plant world is very great In the latter they function not only as a storehouse of carbohydrate food, but also form the chief constituents of cell membrane and supporting tissue, in the animal organism these parts are composed mainly of proteins Polysaccharides of animal origin are built up of glucose alone, those from vegetable sources yield in addition other monosaccharides on hydrolysis

Starch, *amylum*, occurs very widely distributed in the vegetable kingdom Among the raw products used industrially in the preparation of starch may be mentioned the grain or fruit of wheat, maize, rice and horse-chestnut, the tubers of the potato and the pith of the sago palm

[1] Pictet and Vogel, *C r*, 1927, 184, 1512 [2] Kiliani, *Ch Zeit*, 1908, 32, 366 [3] *Tunicin*, an "animal cellulose," occurs in the mantle or leathery skin of the tunicata, found in shallow sea water

In these the starch is stored as granules, which vary in form and size according to the nature of the plant Under the microscope the grains may be seen to consist of an inner nucleus, around which are deposited concentric layers

Starch is a white hygroscopic powder, possessing neither taste nor smell It consists of two very similar polysaccharides, the true starch or *amylose*, present in the interior of the starch cells, and *amylopectin*, contained in the cell walls Starch is insoluble in cold water, but in hot water a paste is formed which rotates the plane of polarisation to the right The formation of the paste is associated with the presence of amylopectin, which contains in addition to carbohydrate a small proportion of combined phosphoric acid The amount of the latter varies with the source of the starch A peculiarity of starch is the blue colour it yields with iodine in the presence of a little potassium iodide or hydriodic acid This is a very sensitive test The colour appears to be due to the adsorption of iodine on the surface of the starch, and not to the formation of a definite compound When boiled with dilute acid, starch is first transformed into a soluble gummy mixture of products known as *dextrin*, and finally into *d* glucose Under suitable conditions the conversion is quantitative Starch also hydrolyses under the influence of certain enzymes, known as *diastases* or *amylases* (see p 137), giving in this case a nearly quantitative yield of maltose This reaction is of great importance in the industrial preparation of alcohol Dextrin is manufactured by heating starch alone, or in the presence of a little nitric acid, to 110°, and is used as a mucilage under the name of "British gum" Concentrated nitric acid dissolves starch with the formation of nitric esters

The starch molecule contains no free carbonyl group, since it yields no compound with phenyl-hydrazine and does not reduce Fehling's solution

Technical Preparation of Starch—The following description gives details of the manufacture of starch from potatoes From other sources it is obtained in a similar manner The starch granules are enclosed comparatively loosely in the cells of the potato, and the process of manufacture consists in rupturing the cell walls and washing the starch grains free from cellulose After being treated in a washing machine, the potatoes are disintegrated, yielding a paste consisting of starch granules, finely divided fibrous tissue, and an aqueous solution containing the juices of the potato This mixture is washed with water in a sifting machine The pulp remaining on the sieves is used as fodder, and the suspension of fibrous matter and starch granules which passes through is allowed to stand for a time, when the specifically heavier starch separates out A little fibrous matter is also carried down by the last layers deposited The starch pulp so obtained is carefully washed, centrifuged, and slowly dried, when it is ready for the market It still contains about 16 to 18 per cent water

As has already been emphasised, starch is one of the most valuable constituents of food, and also forms the basis of the brewing industry and the manufacture of dextrin It is employed in laundry work as a stiffening and for giving a finish

to textiles, as an adhesive (starch paste), as a thickening agent for colours in calico printing, and for sizing paper

Lichenin, *lichen starch*, occurs in many lichens, *e g* Iceland moss On hydrolysis with acids it yields *d* glucose

Glycogen, animal starch or *liver starch* occurs in the animal organism, where, like starch in the vegetable kingdom, it functions as a carbohydrate reserve It can be isolated from liver as a white amorphous powder, but is also present in muscular tissue and in other parts of the organism During muscular effort the glycogen content of the muscle diminishes, owing to its conversion into lactic acid This change occurs through the intermediate formation of *lactacidogen*, a sugar containing combined phosphoric acid On hydrolysis with acids or ferments it finally yields *d* glucose Glycogen differs from starch in dissolving to an opalescent solution in cold water, and in giving with iodine a reddish brown coloration It is very stable towards hot alkalis, and is precipitated with alcohol According to Karrer,[1] glycogen is a polymerised diamylose (see below) of a different degree of polymerisation to starch

Pectins are very complex gelatinising compounds which are found widely distributed in nature, especially in fruit juices They are closely related to the carbohydrates

Constitution of Starch,[2] *Glycogen and Lichenin* —From its behaviour towards amylases starch is believed to be built up quantitatively from maltose residues But proof of a constitutional difference between the two components of starch (p 313) is furnished by treatment with cold concentrated hydrochloric acid In this way Pringsheim isolated two reducing sugars a disaccharide of the composition $C_{12}H_{22}O_{11}$, derived from amylose, and a trisaccharide $C_{18}H_{32}O_{16}$, derived from amylopectin

A further distinction between the interior and the cell walls of starch is shown by their decomposition in the presence of amylases Whereas the amylose readily breaks down quantitatively into maltose, the hydrolysis of the amylopectin is arrested at 65 per cent maltose formation, leaving a trisaccharide trihexosan

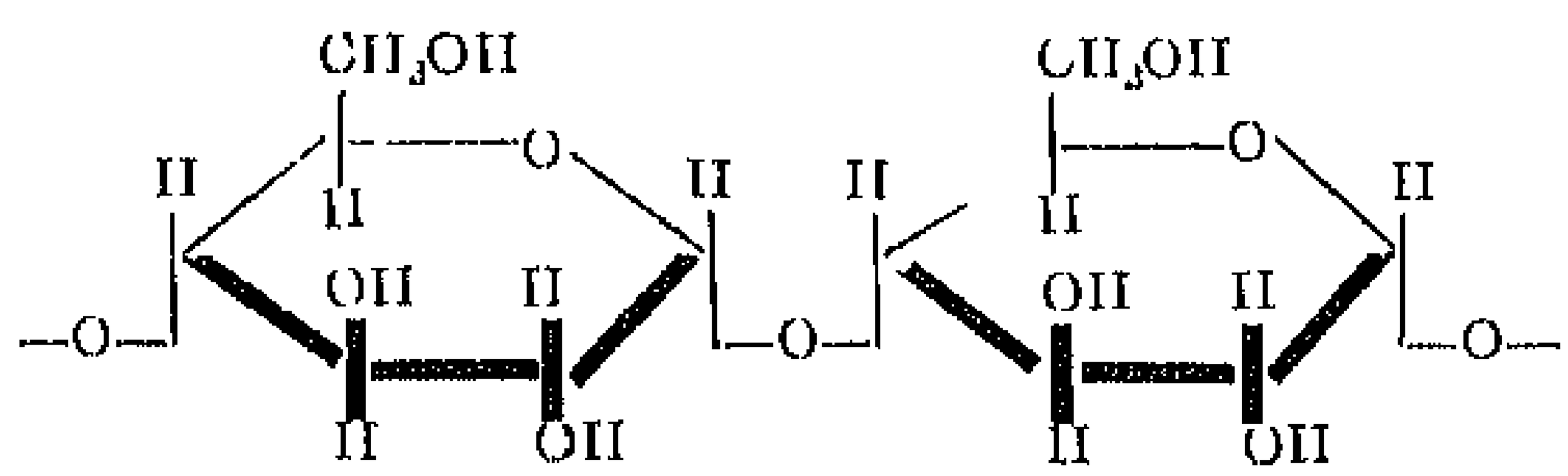
Pringsheim has shown that the two constituents of starch also exist independently in nature The interior substance of the starch cell occurs as lichenin (associated with moss cellulose in Iceland moss) and the material of the cell wall is found in both the animal and vegetable kingdom as glycogen

Glycogen, for example, is quantitatively transformed into glucose on acid hydrolysis, with diastatic ferments it forms maltose Glycogen is also converted into trihexosan by prolonged heating with glycerol at 200° to 210° With cold hydrochloric acid it yields the same trisaccharide as may be obtained from amylopectin Lichenin on the other hand, by similar methods may be converted into dihexosan and the above disaccharide

[1] Karrer and Hoffmann, *Helv Chim Acta*, 1921, 4, 263 [2] P Karrer, *Polymere Kohlenhydrate*, Leipzig, 1926 Haworth and Leitch, *J C S*, 1918, 113, 188, 1919, 115, 809, Irvine and MacDonald, *J C S*, 1926, 128, 1502 H Pringsheim, *Ber*, 1924, 57, 1581, 1926, 59, 3008 J Leibowitz and P Mechlinski, *Ber*, 1926, 59, 2738 M Bergmann, *Ber*, 1926, 59, 2974 K H Meyer, H Hopff and H Mark, *Ber*, 1929, 62, 1103

When *Bacillus macerans* is allowed to grow in a solution of starch, the latter is disrupted to a mixture of products of intermediate complexity termed polyamyloses (Schardinger, Pringsheim). Three of these have been isolated in the crystalline state, viz. α-tetra-amylose $(C_{12}H_{20}O_{10})_2$, β-hexa amylose $(C_{12}H_{20}O_{10})_3$ and an α-hexa- or α-octa-amylose $(C_{12}H_{20}O_{10})_4$, of unknown molecular weight. From their empirical formulæ and the fact that all three are transformed by acetyl bromide quantitatively into maltose or aceto-bromomaltose,[1] these compounds are regarded as polymers of an anhydro-maltose, $C_{12}H_{20}O_{10}$. More recently, by use of acetyl chloride, α tetra-amylose has been converted into the acetyl derivative of a diamylose (a simple anhydride of maltose) and so into diamylose itself, $C_{12}H_{20}O_{10}$.

The actual unit from which starch is built up still remains uncertain. Karrer has suggested that it may be a polymeric form of diamylose, other authors consider the molecule to be built up by ordinary chemical union from an anhydro sugar. Haworth[2] has advanced the view that the starch molecule is composed solely of glucose units joined together by α glucosidic linkings, as illustrated in the following diagram.



Cellulose,[3] possibly of the formula $(C_6H_{10}O_5)_{3n}$, is the most complex polysaccharide known, and forms the chief constituent of the cell walls of all plants. It is therefore obtainable in quantity from many natural products, among which the following rank highest in industrial importance: wood, the chief constituent of which is cellulose; cotton-wool,[4] distinguished by its fineness and comparative purity; also flax, hemp, nettles and other substances. Cellulose possesses an organised tubular structure, which shows distinct minor differences according to the source of the material.

In order to obtain pure cellulose, the cellular tissue of plants, preferably cotton-wool, is treated in succession with dilute alkali, dilute acid, water, alcohol and ether. Under these conditions impurities and incrustations are removed, and the cellulose, which is very stable towards dilute acids and alkalis, is obtained as a white amorphous mass. Textiles such as cotton and linen consist almost

[1] Karrer, *Helv. Chim. Acta*, 1921, 4, 169, 679. [2] *Constitution of Sugars*, p. 83. [3] See *Researches on Cellulose*, 1910–1921, Cross and Dorée (Longmans). [4] Cotton-wool contains in addition to cellulose about $\frac{1}{8}$ or $\frac{1}{7}$ of its weight of some other material. Careful investigation has shown that even the purest and best specimens of cotton-wool do not contain more than 87 per cent. cellulose.

entirely of cellulose, and the finest Swedish filter paper is an almost chemically pure form

Cellulose is insoluble in the usual solvents, including acids and alkalis, but dissolves in *Schweizer's reagent* made by dissolving copper hydroxide in ammonia From this solution cellulose may be precipitated as a jelly by addition of acids, salts, etc, and on washing with alcohol is then obtained as a white amorphous powder A similar solvent power is possessed by a solution of copper carbonate in ammonia, and by zinc chloride dissolved in hydrochloric acid

By suitable treatment with acids, cellulose may be transformed into a hydrated cellulose or *hydrocellulose* This is much more reactive than the original substance, and is therefore frequently used in place of the latter in technical processes requiring cellulose as raw material

With strong sulphuric acid cellulose swells up and passes gradually into solution, from which the addition of water precipitates a substance *amyloid*, resembling starch On prolonged treatment with strong sulphuric acid, followed by boiling with dilute acid, cellulose undergoes complete hydrolysis, yielding first dextrin, and eventually, according to the nature of the cellulose employed, either *d*-glucose alone or a mixture of monosaccharides Under certain conditions the hydroxyl groups of cellulose interact with acids with the production of esters, among which those of nitric acid are of outstanding importance *Acetyl derivatives*[1] of cellulose are obtained by the action of glacial acetic acid and acetic anhydride, and *cellulose aceto-sulphates*[2] by use of a mixture of glacial acetic acid, acetic anhydride and sulphuric acid In these, as in many other cases, mixtures of products are formed showing a progressive increase in the number of substituents entering into the cellulose molecule The change in composition is accompanied by a corresponding alteration in the physical properties of the mixture The central position in the series is occupied by a substance known as "normal aceto-sulphate," analytical results of which are best represented by the formula $(C_{21}H_{28}O_8)(SO_4)(C_2H_3O_2)_{10}$

If well-dried cellulose is brought into an atmosphere containing a small proportion of sulphur trioxide, the latter enters into combination in such a manner that three SO_3 molecules are taken up for each $C_6H_{10}O_5$-group The *acid trisulphate of cellulose* so formed gives well-characterised crystals, which are stable in air and may be obtained analytically pure[3]

$$[C_6H_{10}O_5] + 3SO_3 = [C_6H_7O_5(SO_3H)_3]$$

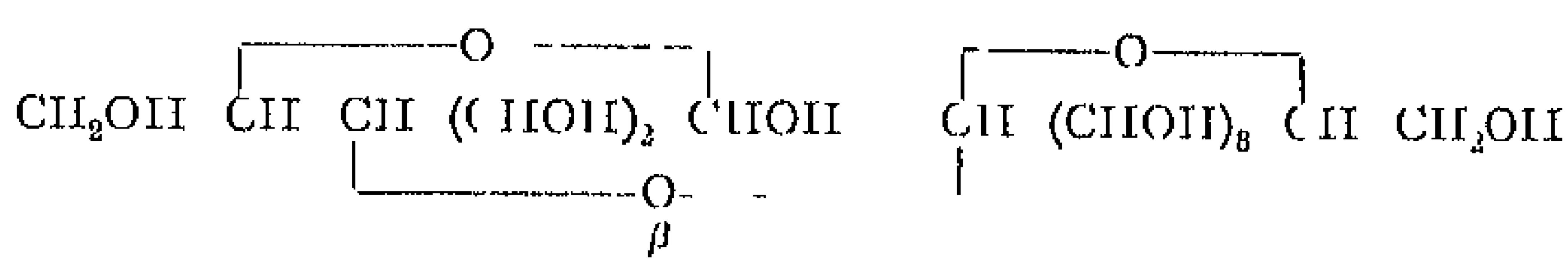
[1] Cross, Bevan and Traquair, *Ch Zeit*, 1905, 29, 527 [2] Cross, Bevan and Briggs, *Ber*, 1905, 38, 1859, 3531 [3] W Traube, Blaser and Grunert, *Ber*, 1928, 61, 754

HYDROLYSIS OF CELLULOSE[1]

Many attempts have recently been made to obtain some knowledge of the constitution of cellulose by the use of hydrolytic methods. In general, the degradation of a complex polysaccharide may be said to be the result of two simultaneous processes: depolymerisation to the fundamental units of the polysaccharide molecule, and disruption of these units to reducing sugars.

In addition to biochemical methods and decomposition under the influence of heat, the following methods have been used for breaking down cellulose into its component parts: hydrolysis with concentrated sulphuric or hydrochloric acid (see below), decomposition with acetic anhydride[2] (*acetolysis*), and decomposition with halogen acids in the presence of an indifferent solvent as diluent.[3] Under these conditions the cellulose is disrupted into glucose and cellobiose (or an isomer, celloisobiose). Fenton and Gostling's method, using dry halogen acids in ethereal solution, finally yields furane derivatives. Dextrins are also important disruption products of cellulose. As yet they can scarcely be defined, but they obviously represent intermediate stages between the cellulose molecule and the simple sugars.

The constitution of cellobiose (cellose) has been recently examined by Haworth,[4] by the method of complete methylation. From an examination of the disruption products of the octa-methyl derivative it is concluded that cellobiose is a glucose-β-glucoside of the structure



Hydrolysis of Cellulose by Concentrated Acids.—Cotton cellulose is only slowly attacked by ordinary concentrated or fuming hydrochloric acid, but it has been shown by Willstätter[5] that an acid saturated at 0°, and containing 40 to 41 per cent HCl, brings about rapid solution. At first the majority of the dissolved product was found to be recoverable on dilution, but in course of time it was hydrolysed to glucose, as shown by an examination of the optical activity and reducing power of the solution. It was estimated on these grounds that an approximately theoretical yield of glucose was produced. More conclusive results have been obtained by Irvine and Soutar[6]

[1] For the X-ray investigation of cellulose see Colloid Symposium Monograph, New York, 1926, 174; Sponsler, *J. Gen. Physiol.*, 1926, 9, 677. Also K. H. Meyer and Mark, *Ber.*, 1928, 61, 593; K. H. Meyer, *Zeit. ang. Chem.*, 1928, 41, 935; Staudinger, *ibid.*, 1929, 42, 37, 67. [2] Irvine, *J. C. S.*, 1920, **117**, 1496; Ost, *Ann.*, 1913, 398, 323. [3] Fenton and Gostling, *J. C. S.*, 1901, 79, 361, 807. [4] Haworth, Long and Plant, *J. C. S.*, 1927, 2809. [5] R. Willstätter and L. Zechmeister, *Ber.*, 1913, 46, 2401; also Ost, *ibid.*, 2995. [6] Irvine and Soutar, *J. C. S.*, 1920, **117**, 1489.

by the use of acetic anhydride and sulphuric acid, and by Monier-Williams[1] using concentrated sulphuric acid alone In the former case a yield of crystalline glucose derivatives was obtained corresponding to 85 per cent of the theory, and in the latter case over 90 per cent of crystalline glucose was isolated, affording strong evidence that the cotton cellulose molecule is entirely built up of condensed glucose molecules

Towards dilute alkalis, which readily dissolve and decompose animal tissue, cellulose is extremely stable A strong solution of caustic alkali, on the other hand, produces a curious thickening and gelatinisation of the walls of the fibre, causing the cellulose to shrink and become translucent This reaction is used for producing crinkled surfaces on cotton fabrics, the process being known as *mercerising*, after its discoverer[2] Alkali celluloses, produced in the above manner by the action of concentrated alkalis, combine with carbon bisulphide to form a mixture of *cellulose xanthates* known as **viscose**[3] These are sodium salts of the general formula RO CS SNa, which swell up with water to a marked degree, giving a colloidal solution which has become of great importance in the manufacture of artificial silk The solution is stable in the cold and in the absence of oxygen, but in air it is gradually decomposed with regeneration of cellulose It is also employed for the impregnation of paper and fabrics, and in calico printing The action of oxidising agents on cellulose leads to the formation of products generally known as *oxycelluloses*

As already indicated, cellulose is used industrially in a variety of ways, *e g* in the preparation of oxalic acid (p 266), paper, parchment paper, collodion, gun-cotton, smokeless powder, celluloid and artificial silk

The following is a short description of the chemical processes involved in the **manufacture of paper** A preliminary treatment is given with the object of effecting a clean separation of the wood cellulose from the encrusting lignin, xylan and other complex substances which cement the cells together into a rigid mass Two processes are in use for the manufacture of paper from wood, straw, esparto grass, etc (*a*) The *caustic soda process*, in which the finely divided wood is boiled (160° to 170°) in iron vessels with dilute caustic soda for several hours under a pressure of 6 to 8 atmospheres Under this treatment certain compounds known collectively under the name of lignin[4] are removed The cellulose is then washed with water and is ready for working up Cellulose which has been purified with caustic soda forms soft threads of small resisting capacity A harder and more valuable product is given by (*b*) the *sulphite process*, in which the

[1] Monier Williams, *J C S*, 1921, 119, 803 [2] In 1844 John Mercer observed that cellulose which had been treated at the ordinary temperature with caustic soda showed, after washing and drying, an increased tenacity and power of taking up certain dyes Later it was found that cotton so treated acquired a higher lustre, and hence mercerisation became an industrial process [3] Cross, Bevan and Beadle, *Ber*, 1893, 26, 1090, 1901, 34, 1513 [4] The presence of lignin in cellulose or paper is easily recognised by the development of a red colour on testing with a solution of phloroglucinol in hydrochloric acid For further information concerning lignin, see E Hagglund, *C*, 1919, III, 186

wood is heated under increased pressure with a solution of calcium or magnesium bisulphite. These reagents also dissolve the enveloping lignin, but have little action on the cellulose fibre.

In the preparation of **parchment paper**, unsized paper (filter paper) is immersed for a few seconds in concentrated sulphuric acid which has been diluted with half its volume of water. It is then washed with water and finally with ammonia. A layer of amyloid is formed on the surface of the paper, rendering it like parchment in appearance, and comparatively impermeable to water.

Cellulose Nitrates, or Nitrocelluloses

A mixture of nitric and sulphuric acids interacts with cotton-wool to form nitric esters of cellulose, incorrectly but very generally known as nitrocelluloses. These still retain the structure of cotton-wool, although somewhat coarser and harder to the touch. By modifying the concentration of acid used and the length of treatment, it is possible within limits to vary the number of nitric acid groups entering into the cellulose molecule. The ester with the lowest proportion of nitrogen has the composition of a dinitrate of cellulose, $C_{12}H_{18}O_8(ONO_2)_2$, while that containing the highest proportion approximates closely to a hexanitrate,[1] $C_{12}H_{14}O_4(ONO_2)_6$. The product obtained, however, is always a mixture, and a gradual alteration of the conditions of nitration never leads to any sudden change in the proportion of nitrogen. No sharp distinction can therefore be drawn between di-, tri- and tetranitrocelluloses, and so on. An important factor is the water content of the nitrating acids; if this is increased, the nitrogen content of the product decreases regularly, although not proportionally, within the above limits. Probably the nitration of cellulose leads to the formation of a mixture of compounds in which a progressively increasing number of complexes have entered into reaction. In addition to esterifying the cellulose, nitric acid also brings about hydration, leading to the formation of hydrocellulose nitrates.

Lower nitrocelluloses containing from two to four nitro groups burn very much more freely than cellulose itself, but are in no sense explosive. They are grouped together under the name of **pyroxylin**, and dissolve readily in a mixture of alcohol and ether, such a solution being sold as *collodion*. The latter is extensively used in medicine, photography and the manufacture of artificial silk (see below).

If lower nitrates of cellulose are mixed with camphor and submitted to the action of heat, **celluloid** is obtained. The warm product is easily moulded, and sets to a hard, transparent mass on cooling. It is employed in the manufacture of a variety of useful and ornamental articles, but is very inflammable.[2]

[1] The actual formulæ of the nitrates are, of course, higher multiples of the above.

[2] Recently a product similar to celluloid has come into use under the name of *galalith*. It is prepared from casein by interaction with formaldehyde, has no odour, and is not dangerously inflammable. *Cellon*, prepared from cellulose acetate (cellite) by the addition of camphor, is also less inflammable than celluloid.

For the preparation of celluloid, 10 parts of nitrated and specially treated tissue paper are intimately mixed with an alcoholic solution of 4 to 5 parts camphor, to which may be added colouring matter. The mixture is kneaded at about 90° in closed iron vessels, rolled out into plates, and thoroughly dried at a moderate temperature.

Celluloid may be considered as an intimate physical mixture of nitrocelluloses and camphor. Nevertheless, its behaviour in some ways resembles that of a true chemical compound, since it no longer possesses the properties of a simple mixture of its components, and can not be separated into the latter by mechanical means without great difficulty.

Owing to the comparatively high price of camphor many attempts have been made to replace it wholly or in part by other substances, but so far no satisfactory substitute has been discovered. Among numerous compounds suggested for this purpose, the most useful appears to be naphthalene.

The highest nitration product of cellulose has a nitrogen content approaching that of a cellulose hexanitrate (p. 319), and is employed under the name of **gun cotton** in propellant explosives and for blasting. Gun cotton burns with extreme rapidity but only explodes when detonated, *e.g.* when combustion is initiated by means of a little mercury fulminate. For explosive purposes it may be used directly in the compressed state, as in torpedoes and in cartridges for blasting, or it may be employed mixed with nitroglycerine (p. 244). A development of great importance is the utilisation of gun cotton and pyroxylin in the preparation of **smokeless powder**. This is based on the fact that when nitrocelluloses are treated with solvents such as acetone or ethyl acetate, even in quantity insufficient for solution, they completely lose their organised structure. Under this treatment they swell up, forming a gelatinous product, which, after removal of the solvent, gives an amorphous mass of the same chemical composition as the starting material, but possessing a much closer texture. In such a product the explosion wave is propagated with much lower velocity, thus rendering it suitable for use as a propellant. Nitrocellulose powders of this type have been adopted by the ordnance departments of almost every army. The explosive is employed in the form of small squares for rifles, and in ribbons or bundles of rods for artillery. In the British and Italian armies, and in certain navies, powders are also in use which contain a considerable proportion of nitroglycerine in conjunction with nitrocellulose.

Nitrocellulose is further of great industrial value in the preparation of artificial silk.

Artificial Silk

The preparation of artificial silk consists essentially in forcing a syrupy solution of cellulose, or certain cellulose derivatives, under high pressure through very fine apertures into a suitable medium, whereby the solvent is removed and fine threads are obtained. The threads are allowed to form under slight tension, and as soon as they have solidified are twisted or collected directly on reels, to be woven subsequently into fabrics in the same way as natural silk.

The practical difficulties of this process were first overcome in 1885 by de Chardonnet, who employed collodion as the starting material. This gave a thread consisting of nitrocellulose and therefore exceedingly inflammable. By treatment with denitrating agents, among which sodium hydrosulphide is

the most suitable, it was found possible to replace the nitrate grouping in the nitrocellulose threads by hydroxyl without altering the form of the material. Threads consisting of cellulose or a hydrate of cellulose are thus produced, which are no more inflammable than ordinary cotton. At the present time large quantities of artificial silk manufactured in this way are used under the name of *Chardonnet* or *collodion silk*.

Cellulose threads possessing the desired silky gloss are also obtained by other methods, *e.g.* by utilising a solution of cellulose in ammoniacal copper oxide as the "spinning liquid" (Pauly's method). In this case the liquid is forced into dilute sulphuric acid, which coagulates the threads and at the same time removes copper and ammonia, yielding without any further treatment a cellulose thread.

A product known as *viscose silk* is manufactured by use of a solution of cellulose xanthates (p. 318). The threads consist at first of viscose, but when dried and submitted to treatment, which need not be described in detail, carbon bisulphide and alkali are eliminated and cellulose is formed.

All these varieties of artificial silk possess a high lustre and pure white colour, and may be obtained without difficulty in all shades by dyeing in the usual manner as for cotton. They have, however, a low tensile strength, especially in the moist state.

Acetate silk, manufactured from acetylated cellulose, possesses a good lustre and great tenacity. It is also insensitive to moisture.

XVIII

Cyanogen Compounds

Cyanogen, *dicyanogen*, *oxalonitrile*, C_2N_2, was discovered in 1815 by Gay-Lussac. It is the first known example of a "compound radical" occurring unchanged throughout a whole series of derivatives, and playing in every case the part of a monovalent element. It behaves in many respects like the halogens, forming, for example, a hydrogen compound HCN, hydrocyanic acid, which strongly resembles the hydrogen halides in its properties.

Cyanogen, $N \equiv C - C \equiv N$, is the nitrile of oxalic acid and can be prepared from ammonium oxalate by heating it with dehydrating agents:

$$C_2O_4(NH_4)_2 - 4H_2O = C_2N_2$$

It is also formed by heating mercuric cyanide, $Hg(CN)_2 = Hg + C_2N_2$. In this reaction a brown amorphous polymer of cyanogen called *paracyanogen* remains behind, the molecular weight of which is unknown. Cyanides of gold and silver decompose in a similar manner under the influence of heat. Cyanogen is usually prepared by heating a solution of copper sulphate with potassium cyanide:

$$2CuSO_4 + 4KCN = Cu_2(CN)_2 + C_2N_2 + 2K_2SO_4$$

It is a colourless, very poisonous gas of pungent smell; it condenses to a liquid at $-25°$, and burns with a bluish-red flame. In aqueous

solution it decomposes rapidly, forming a brown, amorphous mass known as *azulmic acid*[1]

Hydrogen cyanide, prussic acid, HCN, is found in the free state in certain tropical plants, and is formed from the glucoside *amygdalin*, present in bitter almonds, by the hydrolytic action of the enzyme emulsin

$$\underset{\text{Amygdalin}}{C_{20}H_{27}O_{11}N} + 2H_2O = \underset{\text{Benzaldehyde}}{C_7H_6O} + HCN + \underset{d\ \text{Glucose}}{2C_6H_{12}O_6}$$

A very dilute solution of hydrogen cyanide obtained in this manner is used medicinally

Hydrocyanic acid is best prepared by the action of concentrated sulphuric acid (diluted with an equal volume of water) upon a warm strong solution of sodium cyanide Hydrogen cyanide escapes as a gas and can be condensed by use of a freezing mixture

Hydrocyanic acid may also be prepared by heating potassium ferrocyanide with dilute sulphuric acid

$$2K_4Fe(CN)_6 + 3H_2SO_4 = K_2Fe_2(CN)_6 + 3K_2SO_4 + 6HCN$$

Hydrogen cyanide is also formed from acetylene and nitrogen under the influence of the electric arc, and is present in crude coal gas It was originally prepared from Prussian blue, thus giving rise to the terms prussic acid and cyano-compound (from the Greek root signifying "blue")

In the anhydrous state hydrocyanic acid is a colourless liquid with a peculiar smell, reminiscent of bitter almonds It boils at 26°, and solidifies to a crystalline mass at −14° It is one of the weakest acids, and like most cyano-derivatives is exceedingly poisonous Hydrocyanic acid readily combines with water, even on standing in solution, to form ammonium formate, from which it is easily regenerated by distillation On reduction it yields methylamine, $HCN + 4H = CH_3 \cdot NH_2$ It unites directly with the carbonyl groups of aldehydes and ketones (see p 170), and adds on to the double bond of ethylene derivatives Phenyl isocyanate reacts with it to form cyano-formanilide

$$HCN + C_6H_5 \cdot N : C : O = C_6H_5 \cdot NH \cdot CO \cdot CN$$

The addition of HCN to organic compounds is found to be initiated, or greatly accelerated, by the presence of alkalis or organic bases, and on the other hand is prevented or retarded by mineral acids According to Lapworth,[2] this is connected with ionisation and the intermediate formation of complex ions

The *constitution of hydrocyanic acid* as the nitrile of formic acid, $H \cdot C \vdots N$, is deduced from its production from ammonium formate and the ease with which it may be converted into the latter It gives rise,

[1] For the reactions of cyanogen, see Vorländer, *Ber*, 1911, 44, 2455 [2] Lapworth, *Proc Chem Soc*, 1903, 19, 189, 20, 54

however, to two distinct series of alkyl derivatives, namely, the nitriles R C N and the isonitriles R N C or R NC (see p 205), and recently the formula H N C has also been considered for the free acid In any case, the acid must be classed as a liquid tautomeric compound, and hence should be regarded as an equilibrium mixture of the two possible forms HCN and HNC Under ordinary conditions the compound appears to consist almost entirely of the form H C N At higher temperatures the proportion of isonitrile increases somewhat [1]

Simple and Complex Salts of Hydrocyanic Acid—Alkali cyanides are formed on heating nitrogenous organic matter with the requisite metals Like the cyanides of the alkaline earths and of mercury, they are readily soluble in water, whereas the cyanides of the remaining metals are for the most part insoluble

Potassium cyanide can be prepared by heating potassium ferrocyanide in the absence of air

$$K_4Fe(CN)_6 = Fe + C_2 + N_2 + 4KCN$$

It is used as a solvent for silver salts in photography, for the preparation of various double cyanides in electro deposition, and for the extraction of gold When metallic gold dissolves in a solution of potassium cyanide, a double salt of the formula $KAu(CN)_2$ is formed, apparently with absorption of atmospheric oxygen according to the equation

$$2Au + 4KCN + 2H_2O + O_2 = 2KAu(CN)_2 + 2KOH + H_2O_2$$

The hydrogen peroxide set free enables an additional amount of gold to pass into solution

$$2Au + 4KCN + H_2O_2 = 2KAu(CN)_2 + 2KOH$$

Metallic gold may be obtained from the compound $KAu(CN)_2$ by electrolysis or precipitation with metallic zinc

Owing to the demand for potassium cyanide for these purposes, it has recently been prepared synthetically by leading ammonia or nitrogen over a red-hot mixture of charcoal and potassium carbonate Efforts have also been made to prepare it commercially from calcium cyanamide In the former process potassium cyanate is first produced, which is then converted into potassium cyanide, probably as a result of the reducing action of the charcoal

$$K_2CO_3 + NH_3 = KOCN + H_2O + KOH$$
$$KOCN + C = KCN + CO$$

Potassium cyanide is obtained from the crude product by extraction with water, and salting it out of the concentrated solution by addition of potassium carbonate

[1] K H Meyer and Hopff, *Ber*, 1921, 54, 1709

It is almost insoluble in absolute alcohol, but dissolves readily in water. In aqueous solution it rapidly decomposes to give potassium formate and ammonia, $KCN+2H_2O=HCOOK+NH_3$. Its power of undergoing double decomposition with halogen substitution products of organic compounds is frequently used for the introduction of the cyano group. *Silver cyanide*, AgCN, is obtained by precipitating potassium cyanide with silver nitrate. With excess of the first reagent it forms a beautifully crystalline double compound, $KAg(CN)_2$, which is used for electroplating, just as the double cyanides of gold and nickel are employed for the electro-deposition of these metals.

This tendency to form complex salts is characteristic of the cyanides, and in certain cases the metal and cyanogen are united in such a manner that neither of them responds to the usual tests. Among such compounds are *potassium ferrocyanide* or *yellow prussiate of potash*, $K_4Fe(CN)_6+3H_2O$, and *potassium ferricyanide* or *red prussiate of potash*, $K_3Fe(CN)_6$. These are salts of hydroferrocyanic acid, $H_4Fe(CN)_6$, and hydroferricyanic acid, $H_3Fe(CN)_6$, respectively,[1] and are described in detail in text-books of inorganic chemistry. Potassium ferro- and ferricyanides are complex salts containing the electro-negative radical, $Fe(CN)_6$. On ionisation in solution they break up into the complex anions $Fe(CN)_6$ and potassium cations. The ferricyanide is less stable than the ferrocyanide, and for this reason is poisonous, as it decomposes to give hydrogen cyanide when taken internally. It may also be mentioned that potassium ferrocyanide, which is the starting material in the preparation of the above cyanogen compounds, has been obtained from early times by heating nitrogenous animal refuse (such as blood, horn, hoofs, and hair) with potassium carbonate and iron (or iron ore). Recently this method has been abandoned and the salt is now prepared by absorbing hydrogen cyanide in a suspension of ferrous hydroxide or ferrous carbonate in aqueous potassium carbonate, or by treating Prussian blue with potassium hydroxide. Hydrogen cyanide and other cyanogen derivatives are obtained as by-products in the manufacture of coal gas and coke.

Potassium ferricyanide is prepared from potassium ferrocyanide by oxidation with chlorine,

$$2K_4Fe(CN)_6+Cl_2 = 2K_3Fe(CN)_6+2KCl$$

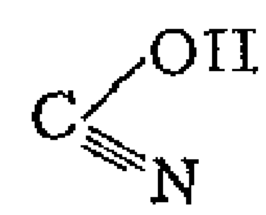
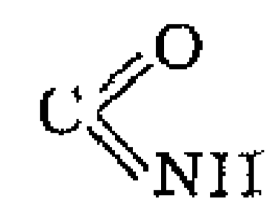
With reference to the constitution of hydroferro- and hydroferricyanic acids, it is assumed by many that both contain the trivalent radical C_3N_3 of cyanuric acid.

Alkyl derivatives of hydrogen cyanide, *i.e.* nitriles and isonitriles, have already been discussed in Chapter XI.

[1] Hydroferricyanic and hydroferrocyanic acids possess in a high degree the property of yielding well defined oxonium salts (p. 151).

Cyanic Acid, Cyamelide, and Cyanuric Acid

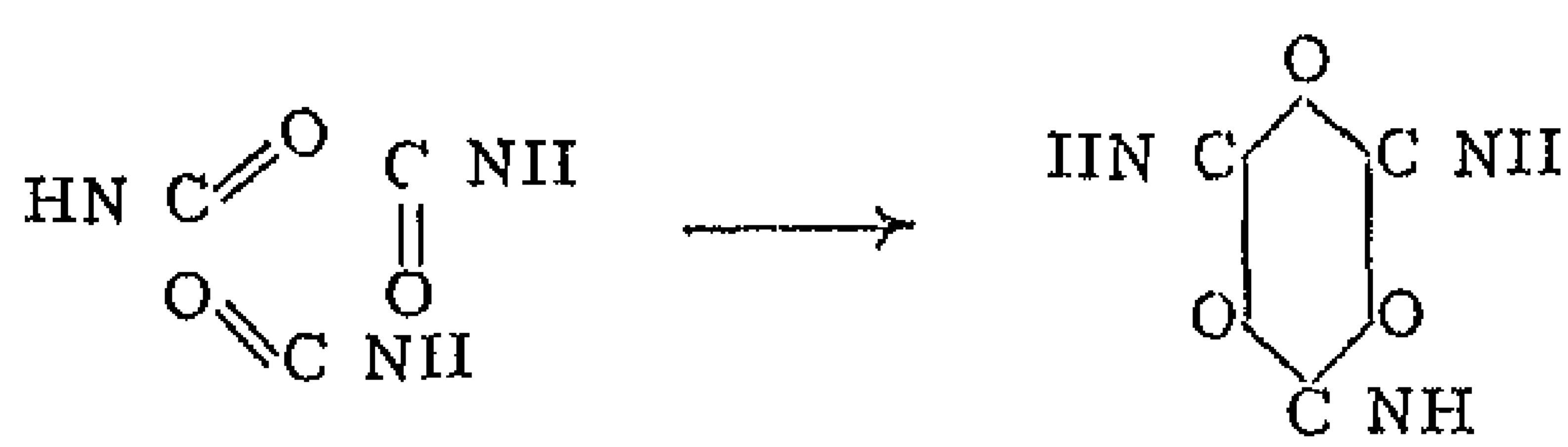
Cyanic acid, HCNO, may be represented by either of the two possible structures I and II

I  II 

Cyanic acid Isocyanic acid

Only one cyanic acid, however, is known This is obtained by the action of heat on cyanuric acid, and forms a colourless liquid which is unstable above 0° As will be seen later, the acid is tautomeric, yielding derivatives corresponding to both of the types I and II In accordance with the modern views on tautomeric fluid compounds, it may be regarded as an allelotropic mixture (p 64) of these two forms[1]

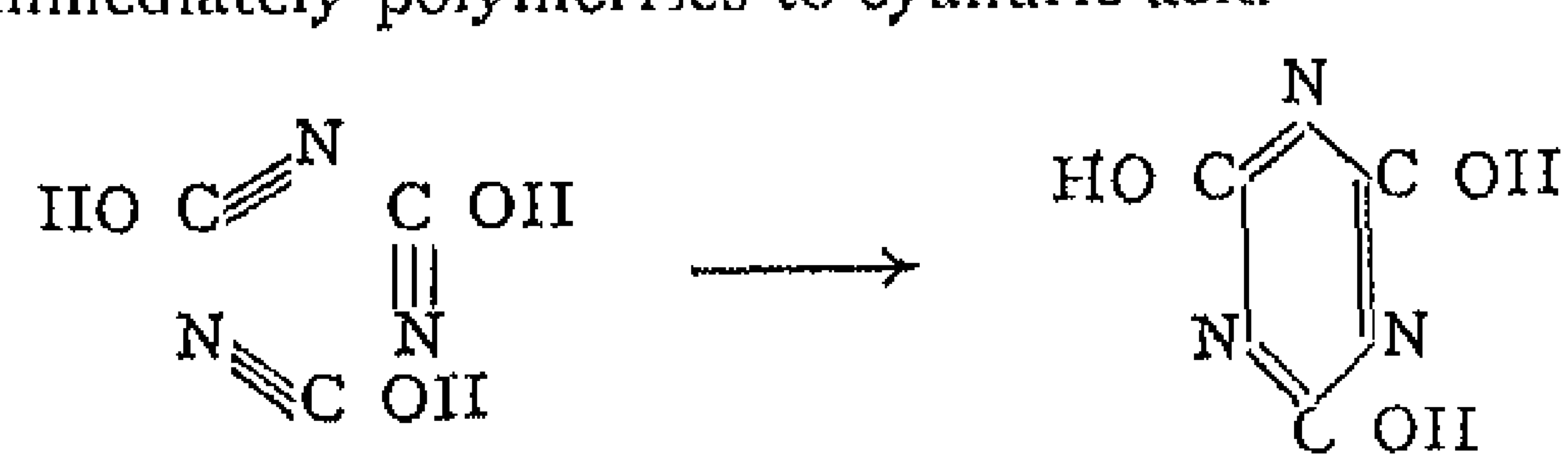
At temperatures above 0°, liquid cyanic acid is transformed with explosive violence into **cyamelide**, of the formula $(CNOH)_3$ This is probably formed by the polymerisation of isocyanic acid, combination taking place between carbon and oxygen in the following manner



Isocyanic acid Cyamelide

Cyamelide is a white, porcelain-like mass which is insoluble in water On being heated it is depolymerised to cyanic acid When heated with water the cyanic acid first produced decomposes slowly into ammonia and carbon dioxide

Cyanuric acid, $(CNOH)_3$, another polymeride of cyanic acid, was discovered long ago by Scheele during the dry distillation of urea, $CO(NH_2)_2$ Under the influence of heat, the urea first breaks up into ammonia and cyanic acid, and the latter, by union between carbon and nitrogen, immediately polymerises to cyanuric acid



Cyanic acid Cyanuric acid

Cyanuric acid is also formed from cyanuric bromide (obtained by the action of bromine on potassium ferricyanide) by warming with water,

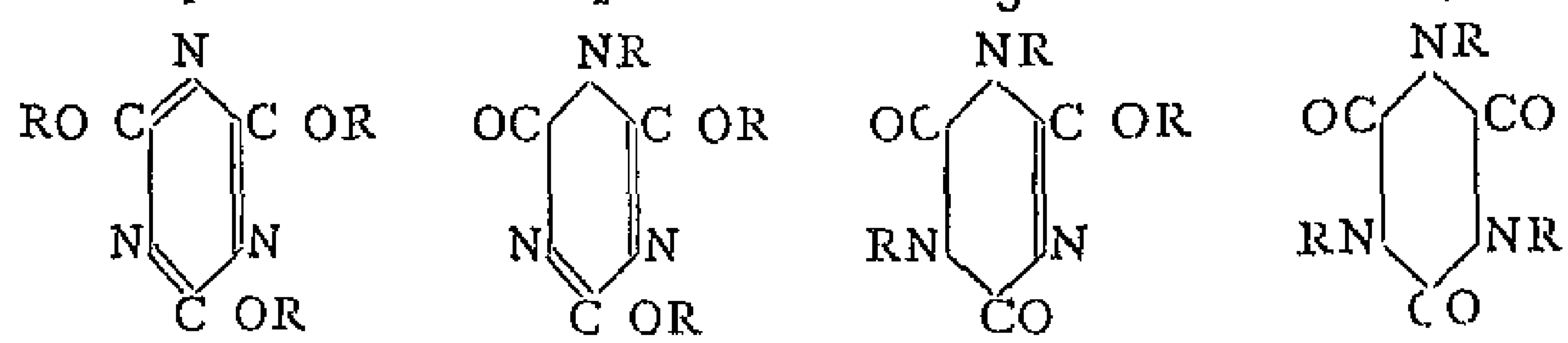
[1] According to Michael and Hibbert, *Ann.*, 1909, 364, 64, cyanic acid possesses the imide structure HN C O in the gaseous state and in certain solvents

and by the isomerisation of cyamelide, which is effected slowly and partially on boiling with water, or more rapidly and completely with alkalis

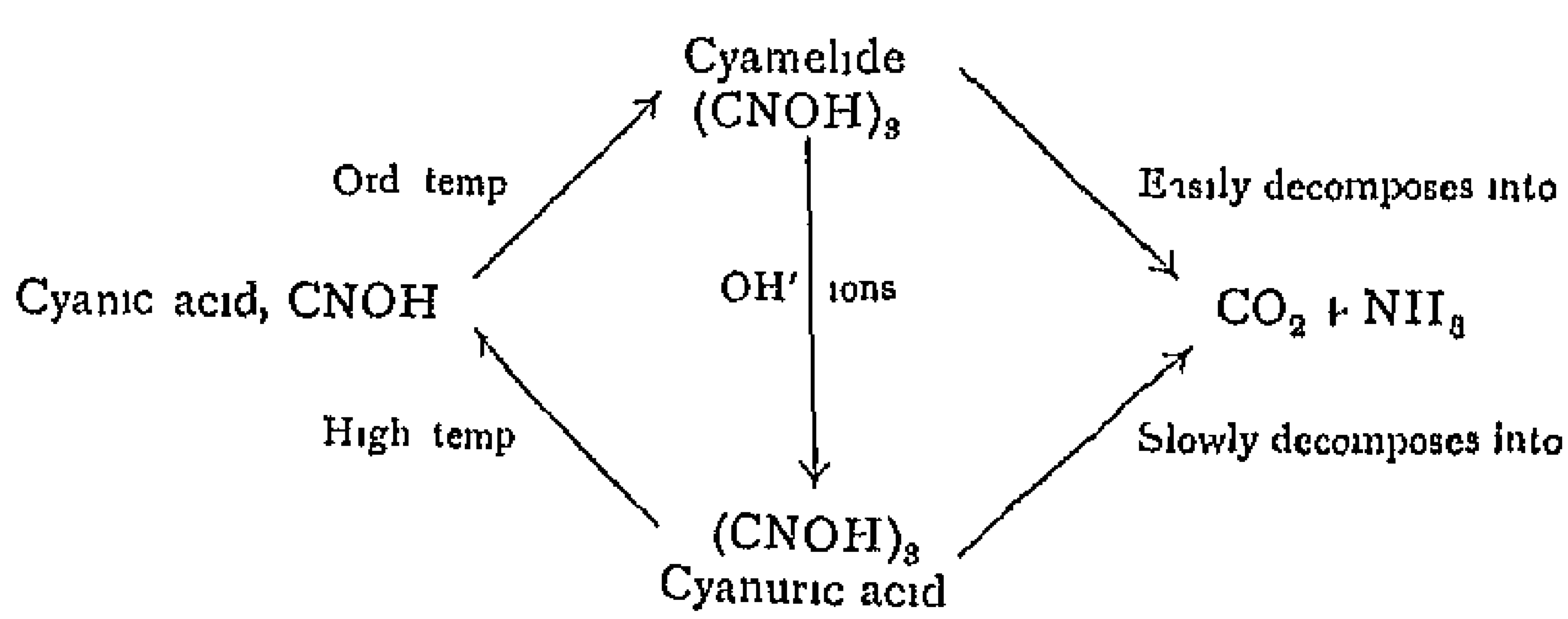
It is a tribasic acid which crystallises in rhombic prisms On prolonged boiling with hydrochloric acid it decomposes into carbon dioxide and ammonia

Cyanuric acid contains the radical $(CN)_3$, in which carbon and nitrogen are linked alternately to form a closed ring The solid acid is a tricarbimide of type 4 (below), and therefore a pseudo-acid Hence it is known as pseudo cyanuric or isocyanuric acid [1] The three pseudo-groups, CO NH, are capable of isomerising into the salt forming groups, C(OH) N, giving rise to four types of derivatives, as illustrated by the following formulæ of the isomeric *trialkyl esters of cyanuric acid* [2]

1 2 3 4



Cyanuric acid and cyamelide are therefore polymerides of cyanic acid possessing different constitutions The relationship between these three compounds is illustrated in the following diagram [2] (Hantzsch)



Derivatives of Cyanic and Isocyanic Acids

A derivative of normal cyanic acid, HO C$\equiv$N, is **cyanogen chloride**, Cl C$\equiv$N, prepared by the action of chlorine on metallic cyanides or hydrocyanic acid, $HCN + Cl_2 = NC\ Cl + HCl$ It is a very poisonous liquid which boils at 14 5°, readily polymerises to cyanuric chloride, $C_3N_3Cl_3$, and on treatment with potassium hydroxide yields potassium chloride and potassium cyanate

$$NC\ Cl + 2KOH = NCOK + KCl + H_2O$$

Esters of normal cyanic acid have not yet been isolated, but **isocyanic esters**, O C NR, derived from the pseudo acid are well known The latter are

[1] Hantzsch, *Ber*, 1906, 39, 139 [2] Hantzsch and Bauer, *Ber*, 1905, 38, 1005

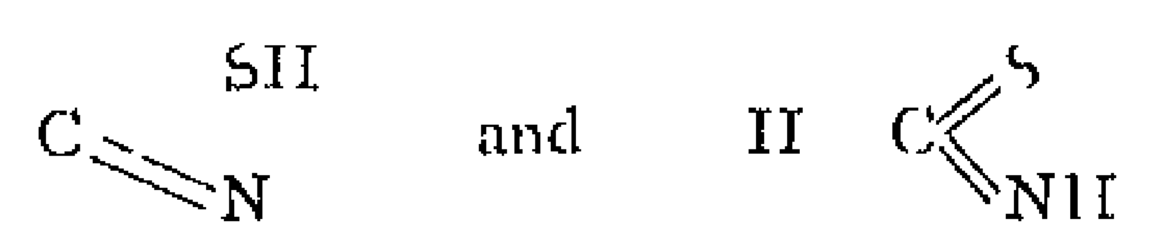
obtained by heating salts of alkyl sulphuric acids with potassium cyanate, or alkyl iodides with silver cyanate (cyanuric esters being also formed).

$$OCNAg + I \cdot C_2H_5 = O : C : N \cdot C_2H_5 + AgI$$

They are liquids of exceedingly pungent smell which boil without decomposition. When heated with alkali they decompose into carbon dioxide and primary amines. With ammonia and amines they unite to form derivatives of urea, $C_2H_5 \cdot NCO + NH_3 = C_2H_5 \cdot NH \cdot CO \cdot NH_2$, and with alcohol to form derivatives of carbamic acid. Esters of isocyanic acid gradually polymerise to cyanuric esters.

Thiocyanic Acid and Derivatives

Thiocyanic acid, *sulphocyanic acid*, HCNS, corresponds to cyanic acid, and like the latter may react in two forms:

I  II

Thiocyanic acid — *Pseudo* thiocyanic acid (Isothiocyanic acid)

Only one thiocyanic acid is known, which may be obtained by treating barium thiocyanate with an equivalent proportion of sulphuric acid, or dry mercury thiocyanate with gaseous hydrogen sulphide. It is a very volatile liquid with an acrid smell, and like cyanic acid readily passes into a solid polymeride. The free acid and its soluble salts give an intense red coloration with faintly acid solutions of ferric salts, a reaction used as a sensitive test for the ferric ion. The colour depends on the presence of the unionised compound, $Fe_2(CNS)_6$.

Potassium thiocyanate, CNSK, is obtained by fusing together potassium cyanide and sulphur. It dissolves readily in water with considerable absorption of heat. *Sodium thiocyanate* occurs in the saliva and urine of various animals. *Ammonium thiocyanate*, $CNS(NH_4)$, is prepared from carbon bisulphide and ammonia.

$$CS_2 + 2NH_3 = CNS(NH_4) + H_2S$$

It forms deliquescent crystals, which on heating at 160° are transformed into thiourea, and at 180° into guanidine thiocyanate. *Silver thiocyanate*, CNSAg, is deposited as a precipitate resembling silver chloride during the volumetric estimation of silver by Volhard's method. *Mercury thiocyanate* may be obtained as a grey amorphous precipitate; when moulded into pellets, dried and ignited, it forms long snake-like tubes of ash (Pharaoh's serpents).

Esters of normal thiocyanic acid, of the formula $N \equiv C—S \cdot R$, are obtained by heating potassium thiocyanate with potassium alkyl sulphates or alkyl iodides.

$$CN \cdot SK + C_2H_5I = CN \cdot SC_2H_5 + KI$$

They are liquids smelling of garlic, and are insoluble in water. On

reduction with zinc and sulphuric acid they yield hydrocyanic acid and mercaptans,

$$CN\cdot S\cdot C_2H_5 + 2H = CNH + HS\cdot C_2H_5$$

and when heated they partially isomerise into isothiocyanic esters

The esters of iso- or pseudo cyanic acid, S : C : N . R, are known as **mustard oils**, and occur in various plants as glucosides of imino-thio-carbonic acid, of the type

$$\text{Glucose}-S-\underset{\substack{|\\ OR'}}{C} = N\cdot R$$

In addition to being formed by isomerisation of the normal esters, they are obtained by the action of mercuric or ferric chloride on amine salts of alkyl dithio-carbamic acids (prepared by the combination of carbon disulphide and amines)

$$2C_2H_5NH_2 + CS_2 \longrightarrow CS\begin{cases} SH,\ NH_2C_2H_5 \\ NHC_2H_5 \end{cases}$$

$$\longrightarrow S : C : NC_2H_5 + H_2S + NH_2C_2H_5$$

They are lachrymatory liquids of extremely pungent odour, which are almost insoluble in water

When heated to 100° with hydrochloric acid or to 200° with water they are hydrolysed to primary amines, carbon dioxide and hydrogen sulphide

$$S : C : N\cdot C_2H_5 + 2H_2O = H_2N\cdot C_2H_5 + CO_2 + H_2S$$

Under the influence of strong sulphuric acid they yield primary amines and carbon oxysulphide

$$S : C : NC_2H_5 + H_2O = H_2NC_2H_5 + S : C : O$$

On reduction they are converted into a primary amine and thio-formaldehyde

$$S : C : NC_2H_5 + 4H = H_2NC_2H_5 + SCH_2$$

These reactions prove that in mustard oils the alkyl groups are linked to nitrogen

The best known representative of this class is **allyl mustard oil** (*ordinary mustard oil*), S : C : N . CH$_2$. CH : CH$_2$, which may be obtained from the seeds of black mustard (*Sinapis nigra*) by distillation with water It is a colourless liquid, b p 148°, the vapour of which is exceedingly pungent and lachrymatory The liquid raises blisters on the skin

Sinigrin, *potassium myronate*, is the parent substance of the natural allyl mustard oil It is a glucoside of the formula $CH_2 : CH\cdot CH_2\cdot N : C\begin{cases} SC_6H_{11}O_5 \\ OSO_2OK \end{cases}$ This structure was first advanced by Gadamer and later confirmed by Schneider and Wrede,[1] who isolated thio glucose from the compound Sinigrin forms white crystals which dissolve readily in water and sparingly in alcohol

[1] W Schneider and Wrede, *Ber* , 1914, 47, 2225

Cheirolin, (γ-thiocarbimido propylmethylsulphone), $CH_3 \cdot SO_2 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot N{:}C{:}S$, the mustard oil of wallflower seed, has been prepared synthetically. It distils at 165° to 168° (6 mm.) as a colourless oil which solidifies to a white crystalline mass of melting point 44°.

Erysolin, $CH_3 \cdot SO_2 \cdot (CH_2)_4 \cdot N{:}C{:}S$, a homologue of cheirolin, has been isolated from the seeds of *Erysimum perowskianum* and also synthesised.[1]

Cyanamide and Derivatives

Cyanamide may react in accordance with either of the formulæ $N{:}C \cdot NH_2$ and $HN{:}C{:}NH$, and it is not known with certainty which of these structures represents the solid compound. It is formed from ammonia and cyanogen chloride, and also by treating thiourea with mercuric oxide or lead hydroxide.

$$\underset{\text{Thiourea}}{NH_2{-}CS{-}NH_2} = \underset{\text{Cyanamide}}{NCNH_2} + H_2S$$

Cyanamide is a colourless crystalline compound, which melts at 40° and readily polymerises. At 150° it is transformed into trimolecular *cyanuramide* or *melamine*, $C_3N_3(NH_2)_3$.

On the one hand it behaves as a weak base, and with strong acids forms salts which are hydrolysed by water. On the other hand it shows the properties of a weak acid, yielding metallic salts such as the technically important calcium cyanamide, and a yellow silver salt which is insoluble in ammonia.

Calcium cyanamide, $CaCN_2$, is prepared by heating a mixture of lime and coke in an atmosphere of nitrogen in an electric furnace.

$$CaO + 2C + 2N = CaCN_2 + CO$$

The product so obtained is extensively used as an artificial manure, as it decomposes slowly with water to give ammonia.

$$CaCN_2 + 3H_2O = CaCO_3 + 2NH_3$$

In this manner it is possible to prepare ammonia indirectly from atmospheric nitrogen, and the process is of great value from the agricultural point of view.

It is also possible to use calcium cyanamide in the preparation of alkali cyanides, which are required in quantity for the extraction of gold. For this purpose the compound is first boiled with water, when dicyandiamide is formed.

$$2CaCN_2 + 4H_2O = 2Ca(OH)_2 + (CN \cdot NH_2)_2$$

The latter, on fusion with a mixture of carbon and soda or potash, is then converted into alkali cyanide and ammonia, melamine also being produced.

$$(CN \cdot NH_2)_2 + Na_2CO_3 + 2C = 2NaCN + NH_3 + H + 3CO + N$$

[1] W. Schneider, *Ann.*, 1910, 375, 207; *Ber.*, 1913, 46, 2634.

Fulminic Acid

Fulminic acid, *carbonyl oxime*, $C:N\cdot OH$, is regarded as the oxime of carbon monoxide,[1] and possesses the properties of a strong acid. It is a very unstable, volatile compound, with a smell recalling that of hydrocyanic acid. Like the latter it is very poisonous. It is formed when fulminates are treated with strong acids and also by the decomposition of formamidoxime (isuretin):

$$\left.\begin{matrix}H\\H_2N\end{matrix}\right\rangle C:NOH \longrightarrow NH_3 + C:N\cdot OH$$

Mercury fulminate, $(CNO)_2Hg$, is the most important of the salts. It was discovered by Howard in 1799, and is largely used in percussion caps as a detonator for explosives. It is prepared technically by dissolving mercury in an excess of strong nitric acid, with the subsequent addition of alcohol. **Silver fulminate** may be obtained in a similar manner; it is much more explosive than the mercury compound, and is used in the manufacture of crackers.

XIX

Derivatives of Carbonic Acid

Carbon dioxide is the anhydride of the very unstable carbonic acid, H_2CO_3 or $O:C(OH)_2$, which may also be considered as hydroxy-formic acid, $HO\cdot COOH$. Owing to the influence of the carbonyl group on the adjacent hydroxyl groups, the acid is dibasic. Carbonic acid and its salts are described in inorganic text-books, and only a few of its derivatives will be treated here.

I.—ESTERS AND ACID CHLORIDE OF CARBONIC ACID.

Esters of carbonic acid, $CO(OR)_2$, are prepared by the action of alkyl iodides on silver carbonate, or of alcohols on carbonyl chloride, $COCl_2$. They are ethereal smelling liquids and are soluble in water, in which they gradually decompose. *Esters of orthocarbonic acid*, $C(OR)_4$, are derived from the hypothetical orthocarbonic acid, $C(OH)_4$, and are formed by the action of sodium alcoholates on chloropicrin, $CCl_3\cdot NO_2$. These are also ethereal smelling liquids.

$$CCl_3\cdot NO_2 + 4NaOCH_3 = C(OCH_3)_4 + 3NaCl + NaNO_2$$

Carbonyl chloride, *phosgene*, $COCl_2$, is produced by direct combination of carbon monoxide and chlorine, and is prepared technically by exposing a mixture of gaseous chlorine and carbon monoxide to the direct rays of the sun. In the laboratory it is more conveniently obtained by the action of sulphur trioxide on carbon tetrachloride:

$$CCl_4 + 2SO_3 = COCl_2 + S_2O_5Cl_2 \quad \text{Pyrosulphuryl chloride}$$

[1] H. Wieland, *Ann.*, 1906, **347**, 233; **350**, 390. *Ber.*, 1907, **40**, 418; 1909, **42**, 820, 1346.

By the use of 45 per cent oleum (pyrosulphuric acid), carbonyl chloride and chlorosulphonic acid are formed almost quantitatively at 78°, according to the equation

$$SO_3 + H_2SO_4 + CCl_4 = COCl_2 + 2SO_3HCl$$

In the presence of catalysts, however, of which infusorial earth is the most satisfactory, the reaction can be brought about by the use of sulphuric acid alone[1]

$$2H_2SO_4 + 3CCl_4 = 3COCl_2 + 4HCl + S_2O_5Cl_2$$

Although a colourless gas at ordinary temperatures, carbonyl chloride readily condenses to a liquid of boiling-point 8°, in which form it is brought on to the market It has a very penetrating, choking smell, readily dissolves in glacial acetic acid, benzene and other hydrocarbons, and owing to the mobility of the chlorine atoms is very reactive When heated with water it decomposes into carbon dioxide and hydrochloric acid, $COCl_2 + H_2O = CO_2 + 2HCl$ With alcohol the first product is *chloro-carbonic ester*,

$$COCl_2 + HOC_2H_5 = Cl \cdot CO \cdot OC_2H_5 + HCl,$$

and finally *carbonic ester*

$$COCl_2 + 2HOC_2H_5 = CO(OC_2H_5)_2 + 2HCl$$

With ammonia it yields *urea*, the *diamide of carbonic acid*,

$$COCl_2 + 2NH_3 = CO(NH_2)_2 + 2HCl$$

Phosgene is employed industrially in the preparation of di- and triphenyl methane dyestuffs

Chloro carbonic esters, also known as *chloro formic esters*, of the general formula Cl CO OR, are produced as mentioned above by the action of alcohols on phosgene They are best obtained by adding the desired alcohol to strongly cooled liquid phosgene They are volatile liquids of pungent smell, which are used for introducing the group —CO OR into organic compounds With organo-magnesium halides they interact to give esters of carboxylic acids

$$R'MgBr + Cl \cdot COOR = R' \cdot COOR + MgClBr$$

II —AMIDES OF CARBONIC ACID

The dibasic nature of carbonic acid is also shown in the formation of two amides, viz, carbamic acid, a mono amide, HO CO NH_2, and urea, a diamide, $CO(NH_2)_2$ With these compounds should be grouped guanidine, $C:NH(NH_2)_2$

Carbamic acid, HO CO NH_2, is not known in the free state, but only in the form of salts and esters *Ammonium carbamate* is produced as a white mass by the combination of dry carbon dioxide and dry ammonia, $CO_2 + 2NH_3 = CO(ONH_4)(NH_2)$, and is present in commercial ammonium carbonate On

[1] Grignard and Urbain, *C*, 1919, III, 989

being warmed to 60° in aqueous solution it takes up a molecule of water and is converted into ammonium carbonate, $CO(ONH_4)(NH_2) + H_2O = CO(ONH_4)_2$

Esters of carbamic acid are known as **urethanes** They may be prepared by the action of ammonia on carbonic or chloro-carbonic esters at the ordinary temperature

$$Cl \cdot CO \cdot OC_2H_5 + NH_3 = NH_2 \cdot CO \cdot OC_2H_5 + HCl$$
$$C_2H_5O \cdot CO \cdot OC_2H_5 + NH_3 = \underset{\text{Ethyl carbamate (urethane)}}{NH_2 \cdot CO \cdot OC_2H_5} + C_2H_5OH$$

also by heating acid azides with alcohols (see p 204)

The urethanes crystallise well, distil without decomposition, and are soluble in alcohol, ether and water With alkalis they decompose into carbon dioxide, ammonia and alcohols, and when heated with ammonia give urea

The compound commonly known as *urethane* is the ethyl ester of carbamic acid, $H_2N \cdot CO \cdot OC_2H_5$ It melts at 50° and boils at 184° When treated with very concentrated nitric acid it yields *nitro urethane*, $NO_2 \cdot NH \cdot CO \cdot OC_2H_5$, from which nitramide was first isolated Urethane is often employed as a narcotic in physiological experiments on the smaller animals

Trichloro ethyl-urethane, $H_2N \cdot CO \cdot OCH_2 \cdot CCl_3$ is used as a hypnotic under the name of "Voluntal" Pharmacologically, it stands between chloral and urethane

Urea, carbamide, $NH_2 \cdot CO \cdot NH_2$, the diamide of carbonic acid, was discovered in urine in 1773, and was the first organic substance to be synthesised in the laboratory (Wohler, 1828) It occurs in the urine of mammals and certain reptiles, and in many other liquids of animal origin A human adult excretes about 30 gms of urea per day, as the decomposition product of proteins

Urea is formed directly by the hydrolysis of egg albumin, serum albumin, casein, gelatin, etc, under the influence of alkali hydroxides, and also, though considerably less rapidly, by use of calcium hydroxide

Urea can be prepared from urine by boiling down to small bulk and adding nitric acid Under these conditions urea nitrate is precipitated, from which, after suitable purification, urea can be liberated by means of barium carbonate

Synthetically, it is obtained by the action of ammonia on phosgene, ethyl carbonate, or urethane These reactions prove the constitution of urea[1]

$$C\begin{cases} Cl \\ O \\ Cl \end{cases} + \begin{matrix} HNH_2 \\ \\ HNH_2 \end{matrix} = C\begin{cases} NH_2 \\ O \\ NH_2 \end{cases} + 2HCl$$
$$CO(OC_2H_5)_2 + 2NH_3 = CO(NH_2)_2 + 2C_2H_5OH$$
$$CO(NH_2)(OC_2H_5) + NH_3 = CO(NH_2)_2 + C_2H_5OH$$

[1] For an alternative constitution of urea advanced by E A Werner, see p 70

It is also formed by the intramolecular rearrangement of ammonium cyanate, when this is evaporated in aqueous solution [1]

$$CON\cdot NH_4 \longrightarrow CO(NH_2)_2$$

This is the epoch-making synthesis of urea effected by Wöhler in 1828, by evaporating an aqueous solution of potassium cyanate and ammonium sulphate. The potassium sulphate which crystallised out on cooling was filtered off and the filtrate evaporated to dryness. From the solid residue thus obtained, urea can be extracted by means of alcohol.

Urea crystallises in long rhombic prisms or needles, which melt at 132°. It dissolves readily in water and alcohol but is practically insoluble in ether. It combines with acids to form salts, of which the most important are the *nitrate*, CON_2H_4,HNO_3, and oxalate. The latter are only sparingly soluble in water or nitric acid, and urea may therefore be precipitated from its solutions in these forms. Urea also yields salts with bases, and combines with certain salts to give crystalline addition compounds. Thus mercuric nitrate yields a precipitate of the composition $2CO(NH_2)_2, Hg(NO_3)_2, 3HgO$, on the formation of which is based a volumetric method of estimating urea (Liebig).

Like other acid amides, urea is readily hydrolysed on being heated with dilute acids or alkalis, or with water above 100°. This decomposition also occurs during the putrefaction of urine, $CO(NH_2)_2 + H_2O = CO_2 + 2NH_3$. When heated alone at 150° to 170°, urea parts with ammonia and is converted into *biuret*

$$NH_2\cdot CO\cdot NH_2 + NH_2\cdot CO\cdot NH_2 \longrightarrow \underset{\text{Biuret}}{NH_2\cdot CO\cdot NH\cdot CO\cdot NH_2} + NH_3$$

Biuret forms colourless needles, melts in the anhydrous state at 190°, and gives a violet coloration with alkali and copper sulphate (see biuret reaction, p. 224). At temperatures above 170° urea yields cyanuric acid. With nitrous acid it reacts to give carbon dioxide, nitrogen, and water, $CO(NH_2)_2 + N_2O_3 = CO_2 + 2N_2 + 2H_2O$. Nitrogen is also liberated by the action of sodium hypochlorite or hypobromite, the complicated reaction which occurs in this case [2] is used in the Hüfner method [3] of estimating urea, by measuring the volume of the nitrogen evolved.

A very convenient and accurate method of estimating urea depends on the action of *urease*, an enzyme occurring in soya beans. This converts urea quantitatively into ammonium carbonate, which can be determined directly by titration, or by liberating the ammonia with potassium carbonate and distilling it over into excess of standard acid.

[1] This process has been shown by J. Walker and Hambly to be a reversible one, *J. C. S.*, 1895, 67, 746. An *N*/10 aqueous solution of urea at 100° gave about 4 to 5 per cent. of ammonium cyanate. The change was followed by use of silver nitrate, which formed the sparingly soluble silver cyanate. [2] See Schestakow, *C.*, 1905, I, 1227. [3] Le Comte, *C.*, 1903, I, 1413. Corradi, *C.*, 1906, I, 1574. Giacri, *C.*, 1914, II, 1, 684.

Alkylated ureas, in which hydrogen is replaced by alkyl radicals, are known in considerable number. They are formed by various methods, *e.g.*, when primary or secondary amines react with potassium cyanate or isocyanic esters.

$$CO{:}NR + NH_2{\cdot}CH_3 = NHR{\cdot}CO{\cdot}NHCH_3$$

In their properties and reactions they strongly resemble urea.

Alkyl isoureas, $HN{:}C(OR){\cdot}NH_2$, derived from an as yet unknown isomeric urea of the formula $HN{:}C(OH){\cdot}NH_2$, are obtained by the union of alcohols with cyanamide, under the influence of hydrochloric acid.

$$C\begin{array}{l}\diagup\!\!\!\equiv N\\ \diagdown NH_2\end{array} + HOCH_3 \;=\; C\begin{array}{l}\diagup OCH_3\\ \;NH\\ \diagdown NH_2\end{array}\ \text{Methyl isourea}$$

Semicarbazide, $NH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$, is formed by the interaction of potassium cyanate and hydrazine hydrate. It is frequently utilised for the detection and isolation of aldehydes and ketones, since the condensation products, semicarbazones, obtained with these compounds usually crystallise well.

$$\underset{\text{Acetone}}{(CH_3)_2C{:}O} + \underset{\text{Semicarbazide}}{H_2N{\cdot}NH{\cdot}CO{\cdot}NH_2} \longrightarrow \underset{\text{Acetone semicarbazone}}{(CH_3)_2C{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2} + H_2O$$

Guanidine, $NH{:}C(NH_2)_2$, may be regarded as imino-urea, or as the amidine of carbamic acid. It is contained in the seeds of the vetch and the juice of the sugar-beet, and is formed when cyanamide is heated with ammonium chloride solution.

$$C\begin{array}{l}\equiv N\\ \diagdown NH_2\end{array} + NH_3HCl \;=\; \left\{C\begin{array}{l}\diagup NH_2\\ = NH\\ \diagdown NH_2\end{array}\right\}HCl$$

Guanidine is generally prepared by heating ammonium thiocyanate at 180° to 190°, when cyanamide occurs as an intermediate product.

$$\underset{\text{Ammonium thiocyanate}}{C\begin{array}{l}\diagup NHNH_3\\ \diagdown\!\!\!\diagdown S\end{array}} \longrightarrow \underset{\text{Thiourea}}{C\begin{array}{l}\diagup NH_2\\ = S\\ \diagdown NH_2\end{array}} \xrightarrow{-H_2S} \underset{\text{Cyanamide}}{C\begin{array}{l}\diagup\!\!\!\equiv N\\ \diagdown NH_2\end{array}} \xrightarrow{+NH_3,\,HCNS} \underset{\text{Guanidine thiocyanate}}{\left\{C\begin{array}{l}\diagup NH_2\\ = NH\\ \diagdown NH_2\end{array}\right\}HCNS}$$

It is a strongly basic crystalline compound, which is readily soluble in water and rapidly absorbs carbon dioxide from the air. It combines with one equivalent of acid to form salts, of which the nitrate, CH_5N_3,HNO_3, is sparingly soluble in water.

When guanidine is treated with a mixture of nitric and sulphuric acids, it is converted into *nitro-guanidine* (I). This is the starting material for the preparation of a number of interesting derivatives of guanidine and urea. On reduction with zinc dust and acetic acid, nitro-guanidine yields *amino-guanidine* (II), which on boiling with acids decomposes into carbon dioxide, ammonia, and *hydrazine* (III).

$$\overset{\text{I}}{HN{=}C\begin{array}{l}\diagup NH{\cdot}NO_2\\ \diagdown NH_2\end{array}} \qquad \overset{\text{II}}{HN{=}C\begin{array}{l}\diagup NH{\cdot}NH_2\\ \diagdown NH_2\end{array}} \xrightarrow{2H_2O} \overset{\text{III}}{H_2N{\cdot}NH_2} + CO_2 + 2NH_3$$

The hydrogen atoms in guanidine can be replaced by alkyl and other radicals An important substitution product of this type has already been met with in *arginine* (see p 220) Two other derivatives are creatine and creatinine

Creatine, *methyl-guanidyl-acetic acid, methyl-glycocyamine,* was synthesised by Volhard from cyanamide and methylamino acetic acid (sarcosine)

$$C{\begin{matrix}\diagup NH_2\\ \equiv N\end{matrix}} + {\begin{matrix}H_3C\\ H\end{matrix}}\!\!>\!N\cdot CH_2\cdot COOH \longrightarrow HN{=}C{\begin{matrix}\diagup NH_2\\ \diagdown N(CH_3)\cdot CH_2\cdot COOH\end{matrix}}$$
$$\text{Creatine}$$

It was discovered by Chevreul in meat broth, and is present in muscle Hence it can be prepared from extract of meat Creatine is a crystalline compound of weak basic properties It has a bitter saline taste and is soluble in water When warmed with dilute acids it loses water and yields creatinine

$$\underset{\text{Creatine}}{\begin{matrix}CH_2 - N{\begin{matrix}\diagup CH_3\\ \diagdown \end{matrix}}C{=}NH\\ |\qquad\qquad\\ COOH\ \ H_2N\diagup\end{matrix}} \;\underset{+H_2O}{\overset{-H_2O}{\rightleftharpoons}}\; \underset{\text{Creatinine}}{\begin{matrix}CH_2 - N{\begin{matrix}\diagup CH_3\\ \diagdown \end{matrix}}C{=}NH\\ |\qquad\qquad\\ CO - HN\diagup\end{matrix}}$$

Creatinine is found in urine and in muscle It is strongly basic and has an alkaline reaction in aqueous solution By combination with water it may be converted into creatine

Creatine phosphoric acid, phosphagen, probably having the structure[1]
$HN{=}C{\begin{matrix}\diagup NH-PO_3H_2\\ \diagdown N(CH_3)\cdot CH_2\cdot COOH\end{matrix}}$, has recently been shown by Ph and G P Eggleton[2] to be a physiologically important constituent of muscle tissue It may be regarded as the parent substance of the creatine in the muscle In the muscles of crustaceans, in which creatine is absent, the place of phosphagen is taken by *arginine phosphoric acid*[3] Each of these compounds is characterised by the mobility of the acid amide linking, the phosphoric acid being rapidly and completely removed in the presence of dilute mineral acids, even in the cold

III —SULPHUR DERIVATIVES OF CARBONIC ACID.

Carbon oxysulphide, COS, is formed by leading a mixture of carbon monoxide and sulphur vapour through a red hot tube, and by the action of hydrogen sulphide on isocyanic esters

$$2OC{:}N\cdot C_6H_5 + H_2S = COS + CO(NH\cdot C_6H_5)_2$$

It is a colourless combustible gas of unpleasant odour, which is decomposed slowly by water and rapidly by alkalis to give carbon dioxide and hydrogen sulphide, $COS + H_2O = CO_2 + H_2S$

Carbon subsulphide, C_3S_2, may be prepared by various methods from carbon disulphide It is a reddish strongly refracting liquid,[4] which solidifies below 0°

[1] C Fiske and Subbarow, *Science*, 1927, 65, 401 [2] Ph Eggleton and G P Eggleton, *Biochem Journ*, 1927, 21, 190 [3] O Meyerhof and Lohmann, *Biochem Zeitschr*, 1928, 196, 49 [4] *Ber*, 1912, 45, 3568

Carbon disulphide, CS_2, is prepared industrially by leading sulphur vapour over wood charcoal or coke at a red heat, and after fractionation is obtained as a colourless strongly refracting liquid of boiling-point 46° and sp. gr. 1.27. It has an unpleasant smell, a sharp taste, and is very inflammable, burning with a blue flame to give carbon dioxide and sulphur dioxide, $CS_2+3O_2=CO_2+2SO_2$. Carbon disulphide is insoluble in water, but mixes in all proportions with alcohol and ether. It is a good solvent for iodine, sulphur, phosphorus, vegetable oils and resins.

The following are the more important of its chemical reactions. Chlorine or bromine in the presence of a halogen "carrier" converts it into carbon tetrachloride or tetrabromide. On treatment with an alcoholic solution of potassium hydroxide it forms *potassium xanthate*, which crystallises in brilliant yellow needles.

$$CS_2+KOC_2H_5 = C\begin{cases} OC_2H_5 \\ S \\ SK \end{cases}$$

Free *xanthic acids*, of the general formula RO.CS.SH, are very unstable. The name is derived from their property of giving *yellow* precipitates of cuprous xanthates with copper salts.

Carbon disulphide finds a number of uses. Owing to its great solvent power it is employed for extracting sulphur from sulphur ores and coal gas purification residues, and fats and oils from seeds, bones and other materials. It is also the starting material in the manufacture of potassium xanthate (used for destroying the vine louse), carbon tetrachloride, and cellulose xanthates (viscose, pp. 318 and 321).

Thiourea, *thiocarbamide*, $NH_2.CS.NH_2$, is formed from ammonium thiocyanate by an intramolecular change similar to the urea transformation. In this case, however, the reaction takes place less readily (170° to 180°), and is also less complete, owing to the thiourea reverting to thiocyanate.

$$CSN.NH_4 \rightleftarrows CS(NH_2)_2$$

Thiourea crystallises in rhombic prisms, m.p. 172°, and dissolves readily in water or hot alcohol, but only sparingly in ether or cold alcohol. When boiled with acids or alkalis it decomposes into carbon dioxide, ammonia and hydrogen sulphide, $CS(NH_2)_2+2H_2O=CO_2+2NH_3+H_2S$. Oxides of silver, mercury or lead remove hydrogen sulphide, even at the ordinary temperature, and yield cyanamide.

$$CS(NH_2) = NC.NH_2+H_2S$$

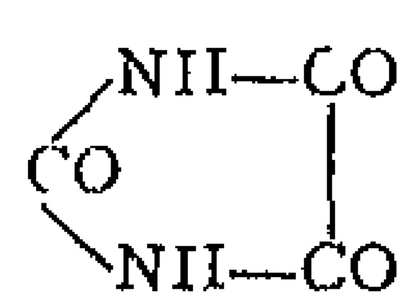
Like urea, it is a tautomeric substance,[1] and may react according to either of the formulæ $NH_2.C\begin{cases} NH_2 \\ S \end{cases}$ or $HN:C\begin{cases} NH_2 \\ SH \end{cases}$

[1] Werner, *J. C. S.*, 1912, **101**, 1167, 1982, 2116, 2180.

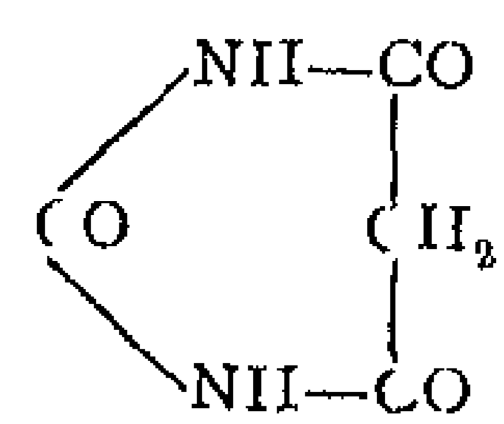
XX

Ureides and Purine Derivatives[1]

Dibasic acids unite with urea in the same manner as with ammonia, to form compounds of the amide type. When one carboxyl group alone enters into reaction, with loss of one molecule of water, the resulting compounds are known as **ureido-acids**. If both carboxyl groups take part, with elimination of two molecules of water, there are formed cyclic derivatives of urea known as **ureides**.[2] Of these two groups, the ureides are the more important, as they are closely related to a number of complex products, such as uric acid, which occur in animal and vegetable organisms as a result of protein decomposition. From the typical ureides, oxalyl urea and malonyl urea, can be derived all the members of the uric acid group.



Oxalyl urea
or parabanic acid



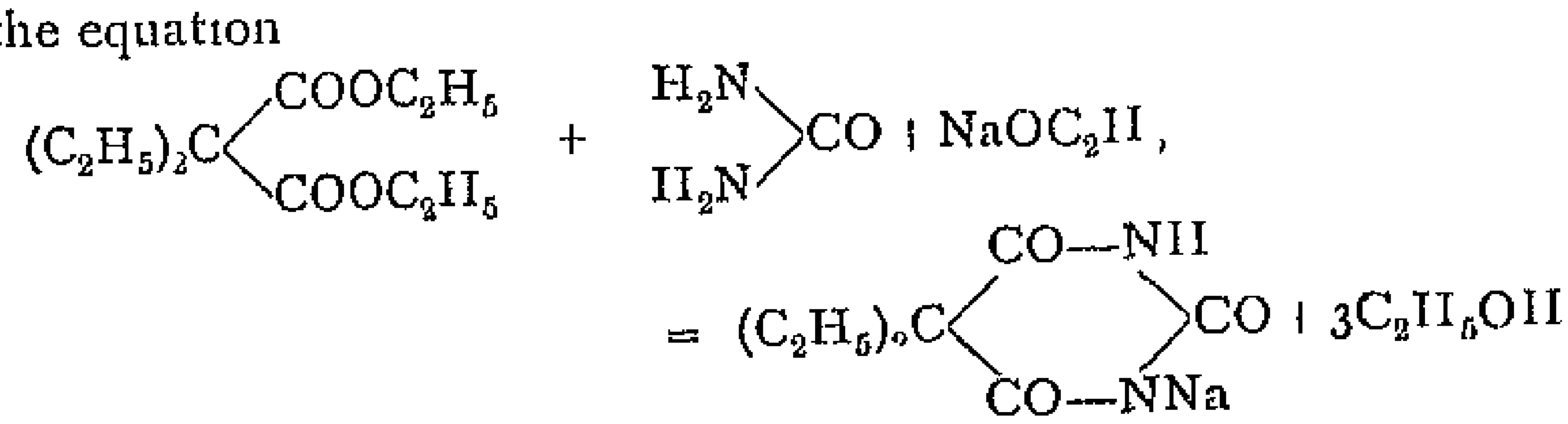
Malonyl urea
or barbituric acid

Malonyl urea is of special interest, as it was from one of its simple derivatives, pseudo-uric acid, that Fischer succeeded in synthesising uric acid itself. Other derivatives of malonyl urea are dialuric acid (hydroxy-malonyl urea), alloxan (dihydroxy-compound), violuric acid (nitroso compound), dilituric acid (nitro compound), and uramil (amino-compound).

***C*-Diethyl barbituric acid, veronal**, was isolated in 1882 by Conrad and Guthzeit, by the action of ethyl iodide on the silver salt of barbituric acid. It was not until 1903 that Fischer and Mehring showed that it was an excellent hypnotic. Since then this substance, which is used in medicine under the name of veronal, has become of great interest to the chemical and medical world and has given rise to an extensive scientific and patent literature. Veronal can be prepared by condensing the ester of diethyl-malonic acid with urea in the

[1] F. Fischer, *Ber.*, 1899, 32, 435. Also "Untersuchungen in der Purin Gruppe" (Springer, Berlin, 1907). [2] Although these compounds are cyclic, the ring systems are comparatively easily opened. In addition, their properties and methods of formation are so closely related to those of open chain products that they are more conveniently described at this stage than under the heading of heterocyclic compounds, where they properly belong.

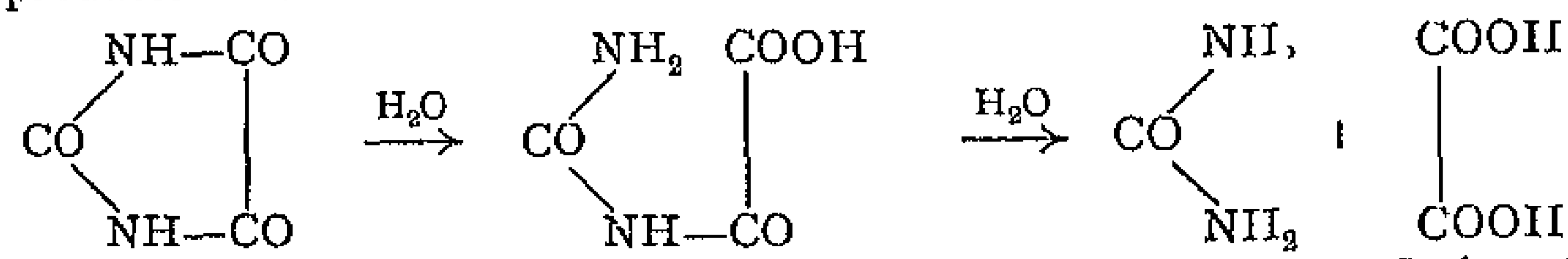
presence of sodium ethylate, the sodium salt being formed according to the equation



Sodium salt of veronal

Esters of mono-alkylated malonic acids may also be condensed in the same manner

The ureides are for the most part beautifully crystalline compounds whose character as amides is shown by the fact that on prolonged warming with dilute alkalis they take up two molecules of water to yield a dibasic acid and urea Ureido-acids occur as intermediate products in this reaction

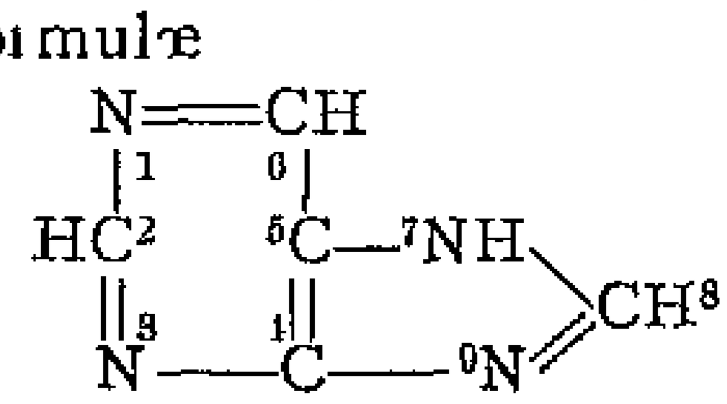
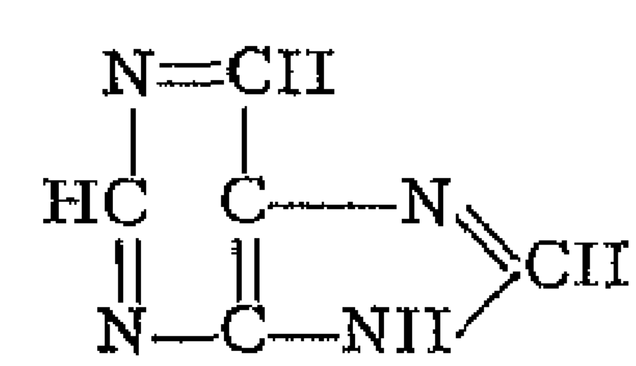


Oxalyl urea Oxaluric acid Urea Oxalic acid

Ureides are acidic in character and form salts in which the imido hydrogen is replaced by metals

Uric acid and other closely related compounds described here are termed *diureides*, as they contain two urea residues—NH CO NH—in the molecule All are derived from the same parent compound, which Fischer has named **purine**

The structure of purine may be represented by either of the two following formulæ

I  II 

and we are therefore dealing with a case of tautomerism recalling that of the amidines This peculiarity repeats itself in all those purine derivatives in which no oxygen is present in the five-membered ring In the following pages, formulæ of the type I will be adopted for free purine and all similar compounds

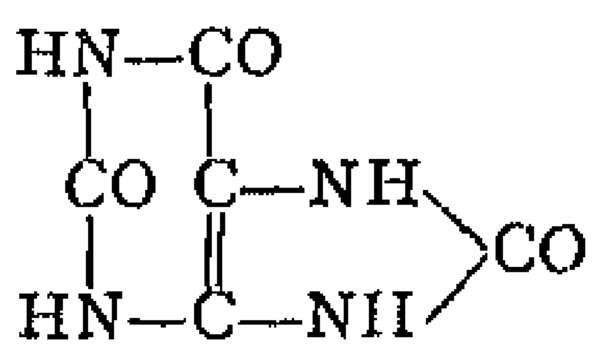
Purine itself has been obtained from 2 6 8 trichloro purine, which is described later The latter was partially reduced to di iodopurine by treatment with hydriodic acid and phosphonium iodide at o°,

$$C_5HN_4Cl_3 + 4HI = C_5H_2N_4I_2 + 3HCl + 2I$$

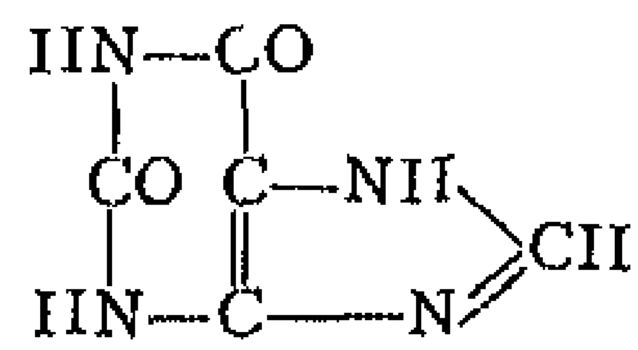
and this on reduction with zinc dust and water gave purine It is a beautifully crystalline substance, m p 211 to 212°, which is readily soluble in water and forms salts with both acids and bases

In order to build up a systematic nomenclature for the numerous compounds of this class, Fischer numbered the atoms of the purine molecule as in the above formula and denoted the position of substituent groups in the usual manner. Old-established names such as uric acid, xanthine, etc., are, however, still in common use.

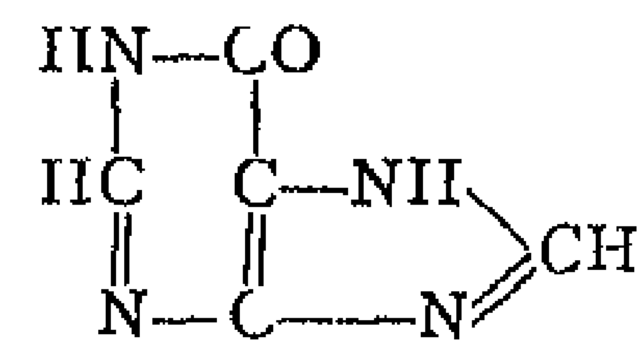
The following summary shows the close relationship existing between a number of these compounds:



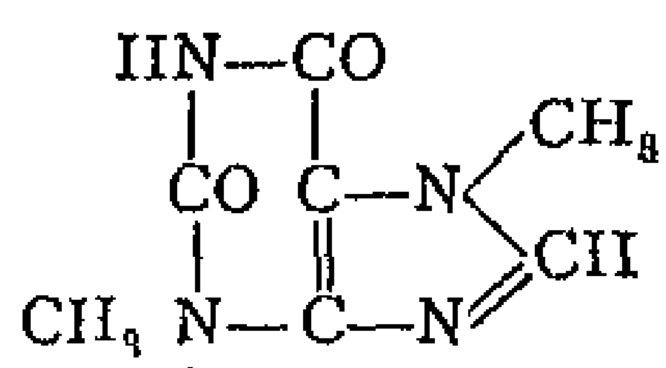
Uric acid,
2, 6, 8-trihydroxy-purine



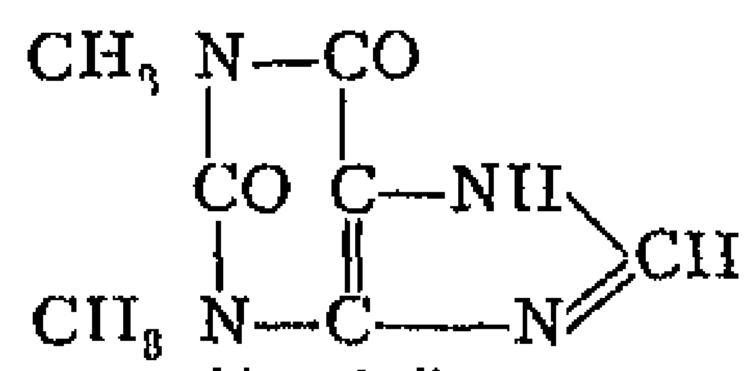
Xanthine,
2, 6-dihydroxy-purine



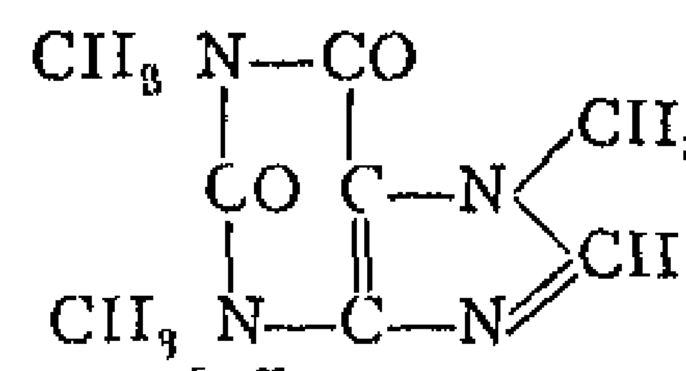
Hypoxanthine,
6 hydroxy-purine



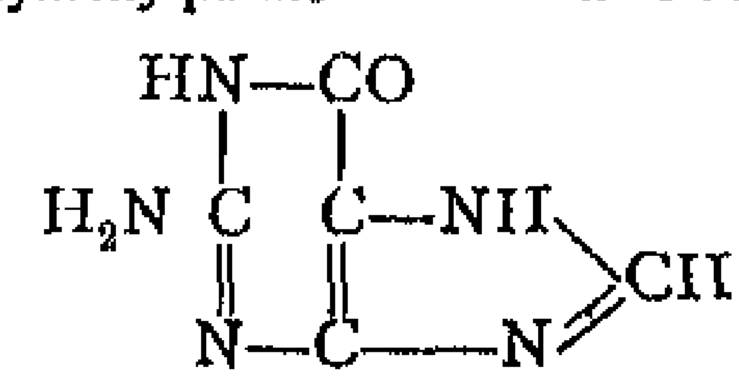
Theobromine,
3, 7-dimethyl-
2, 6 dihydroxy purine



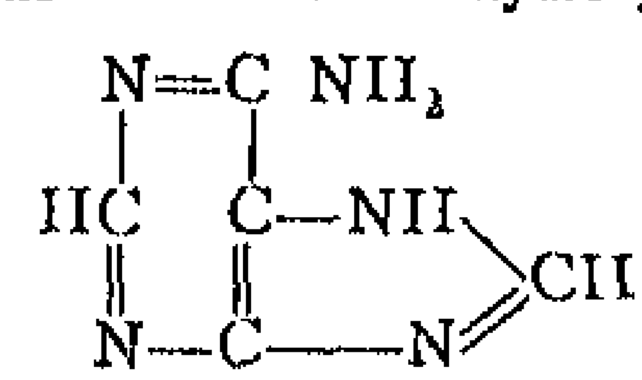
Theophylline,
1, 3-dimethyl-
2, 6-dihydroxy-purine



Caffeine,
1, 3, 7-trimethyl-
2, 6-dihydroxy-purine



Guanine,
2-amino 6 hydroxy purine



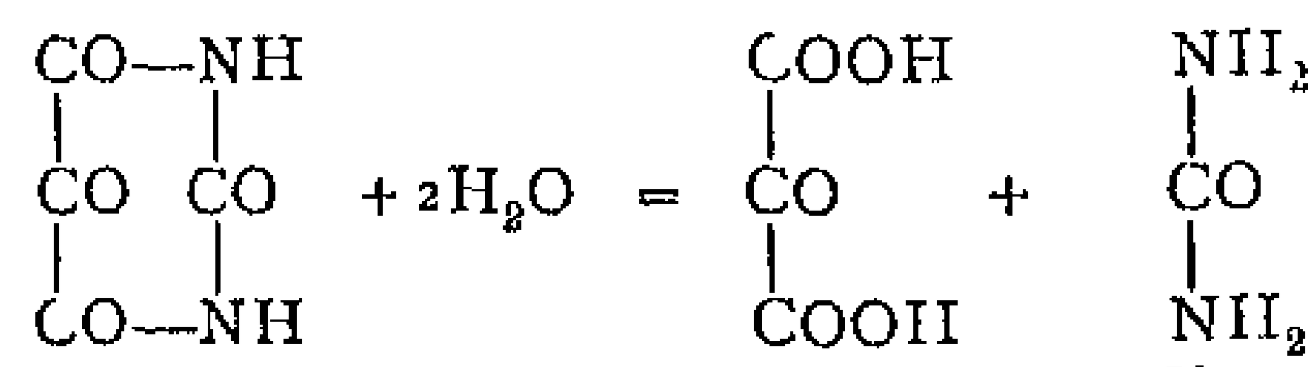
Adenine,
6-amino purine

Uric acid, *2, 6, 8 trihydroxy-purine*, $C_5H_4N_4O_3$, was discovered in 1776 by Scheele in urinary calculi and in human urine. Later it was found by Fourcroy and Vauquelin in the excrement of birds, and in particularly large quantities (25 per cent of the total weight) in the guano of the South Sea Islands. It is also present in the excrement of snakes.

The latter sources consist chiefly of ammonium urate and may be used for the preparation of the acid. Uric acid is a white crystalline powder, very sparingly soluble in hot water, and practically insoluble in cold. As a weak dibasic acid it forms two series of salts, which are almost all difficultly soluble. In gouty patients, uric acid separates out in the joints in the form of sparingly soluble acid salts. Water containing lithium salts or piperazine were formerly employed as a remedy, on account of the higher solubility of the urates of lithium and piperazine.

Reactions of Uric Acid.—Uric acid readily undergoes oxidation; under most conditions the elements of water are also taken up, with the elimination of first one urea residue and finally the second

1 By moderate oxidation with nitric acid, uric acid yields urea and *alloxan*; consequently the atomic framework of the latter compound must be present in uric acid. The constitution of alloxan as *mesoxalyl urea* follows from its decomposition with alkalis

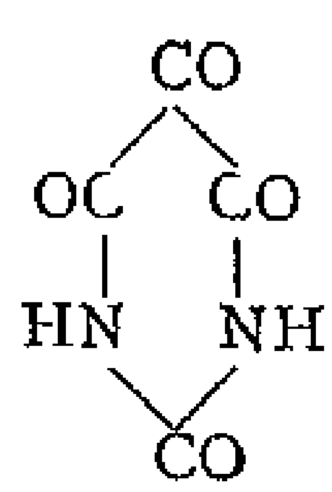


Alloxan Mesoxalic acid Urea

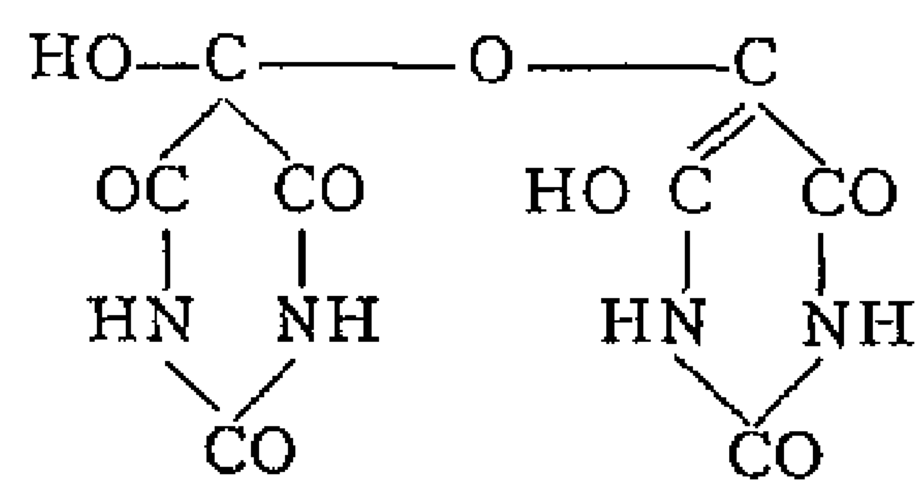
By more energetic treatment with nitric acid, the alloxan first produced is converted into *parabanic acid* or *oxalyl urea* (see p. 337), together with carbon dioxide and ammonia.

With reducing agents alloxan yields alloxantin, which, with ammonia, gives *murexide*, the ammonium salt of purpuric acid. Murexide crystallises in greenish gold prisms and dissolves in water to a purple solution. It may be used for the identification of uric acid and urates, since alloxantin is also formed directly from uric acid by evaporation with dilute nitric acid.

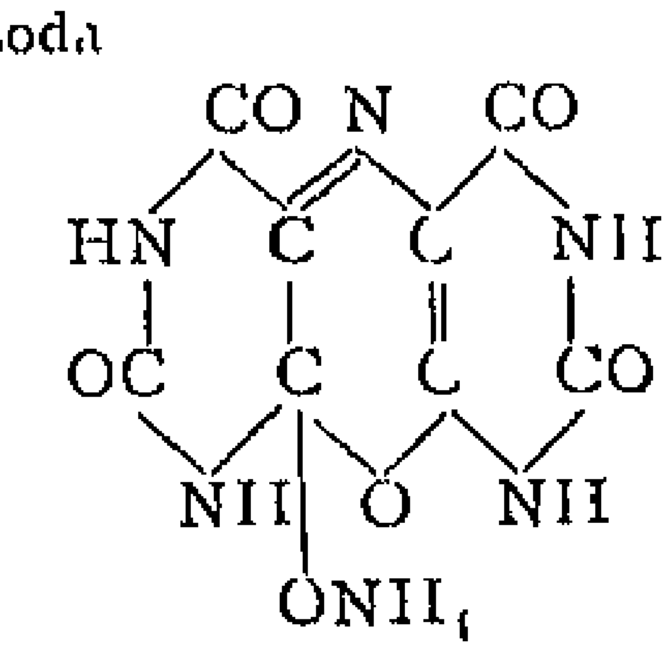
The *murexide test* is carried out by adding a little dilute nitric acid to a few crystals of uric acid and carefully evaporating to dryness. The red residue becomes purple on the addition of ammonia, and blue with caustic soda.



Alloxan

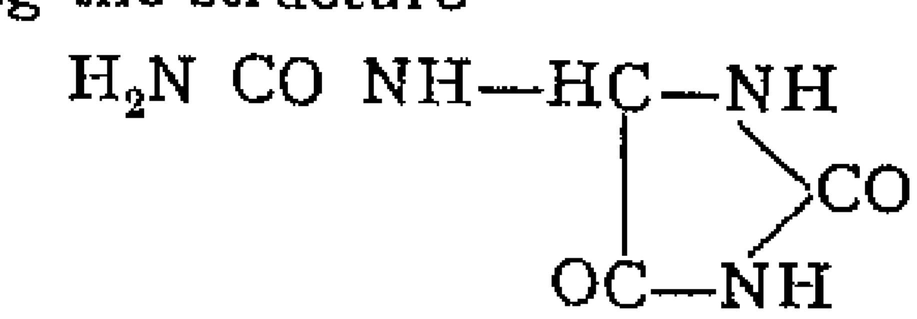


Alloxantin [1]



Murexide (?)

2 The oxidation of uric acid with alkaline permanganate leads through several intermediate products to the formation of *allantoin*,[2] so that the five membered ring of this compound must also be contained in uric acid. The formulation of allantoin as a ureide of glyoxalic acid, having the structure



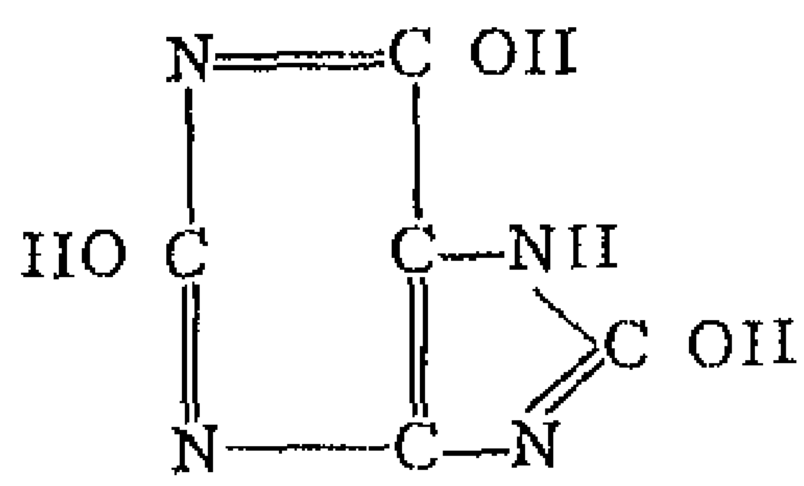
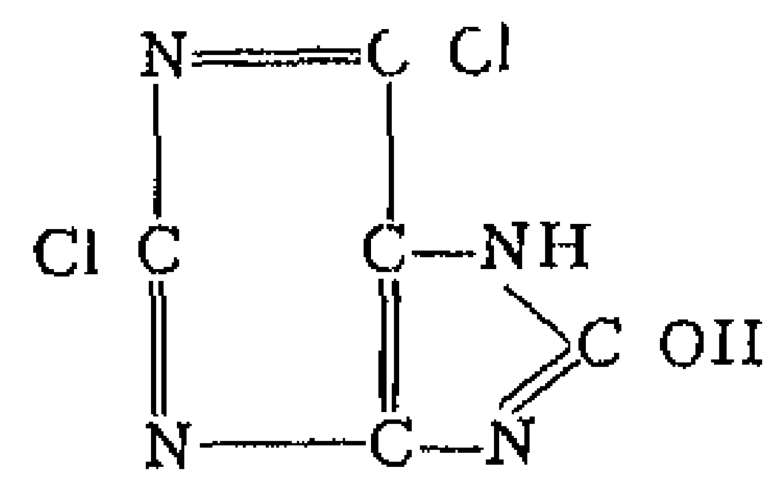
Allantoin

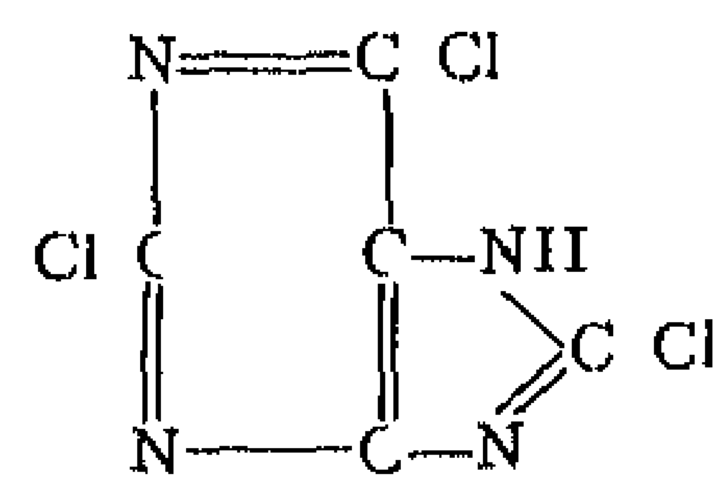
is based on its synthesis from glyoxalic acid and urea at 100°.

The reactions quoted under 1 and 2 confirm the above formula for uric acid, which was first put forward by Medicus on general grounds,

[1] O. Piloty, *Ann.*, 1904, 333, 22. For objections against the above formula, see Möhlau, *Ber.*, 1904, 37, 2686; Slimmer and Stieglitz, *Am. C. J.*, 1904, 31, 661. [2] *Allantoin*, m.p. 238-240; occurs in the urine, especially of carnivorous animals, and is widely distributed in the vegetable kingdom. In many animals it is eliminated in the urine as the end product of nitrogen metabolism, thus playing a similar rôle to uric acid in the human organism. It crystallises in prisms which are sparingly soluble in cold water.

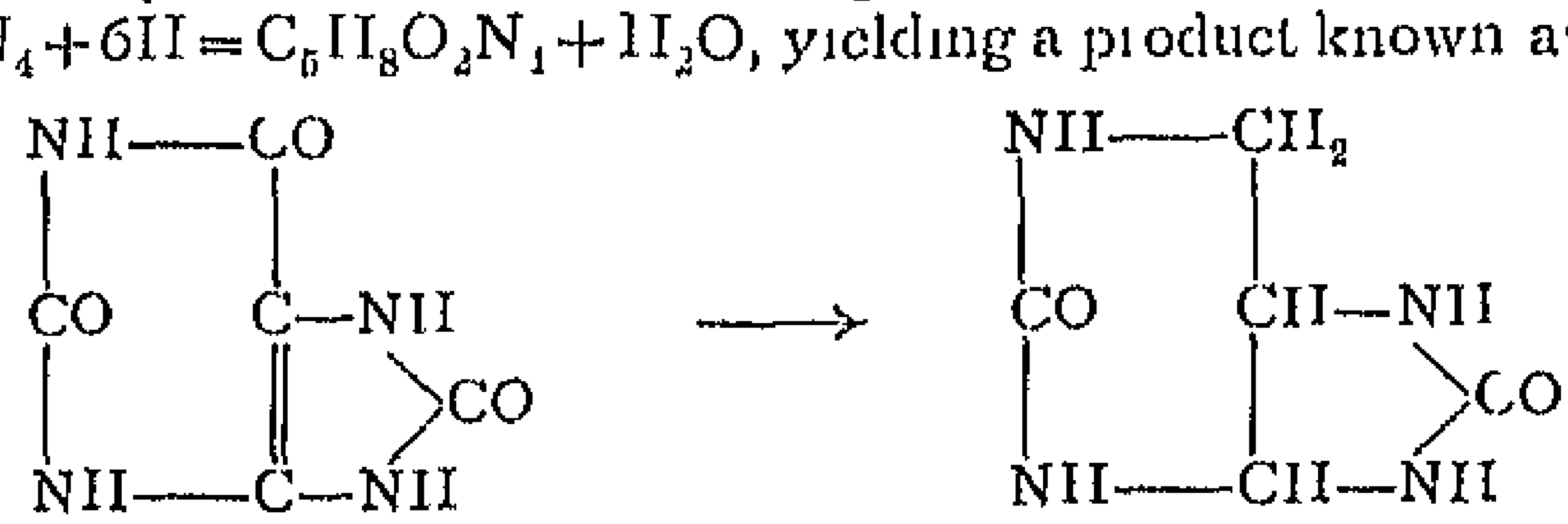
and later established by E Fischer[1] by his investigations on the methyl derivatives of uric acid and by synthesis Before describing the synthesis of uric acid, the behaviour of the compound towards phosphorus oxychloride may be noted With this substance it reacts in the tautomeric form (I), being converted first into 2 6-dichloro-8-hydroxy-purine (II), and finally into 2 6 8 trichloro-purine (III)

I  II 

III 

These chloro-compounds, and particularly 2 6 8-trichloro-purine, are of great importance for the synthesis of other purine derivatives from the comparatively cheap uric acid The chlorine atoms are very reactive, and can readily be exchanged for the groups C_2H_5O—, HO—, HS—, H_2N—, I—, and also in part by hydrogen[2] In this way it is possible to obtain a large variety of derivatives in addition to naturally occurring products Synthesis has far outstripped nature in this respect In place of the few naturally occurring purine derivatives known at the beginning of these researches, there now stand about 150 synthetic products, and Fischer's methods, according to his own estimate, would produce without difficulty twice or thrice this number Physiology and medical practice have derived great benefit from these investigations Owing to their medicinal value, *caffeine, theobromine,* and *theophylline* are now prepared industrially by Fischer's method, from the uric acid of guano

The electrolytic reduction of uric acid proceeds according to the equation $C_5H_4O_3N_4 + 6H = C_5H_8O_2N_4 + H_2O$, yielding a product known as *purone*[3]

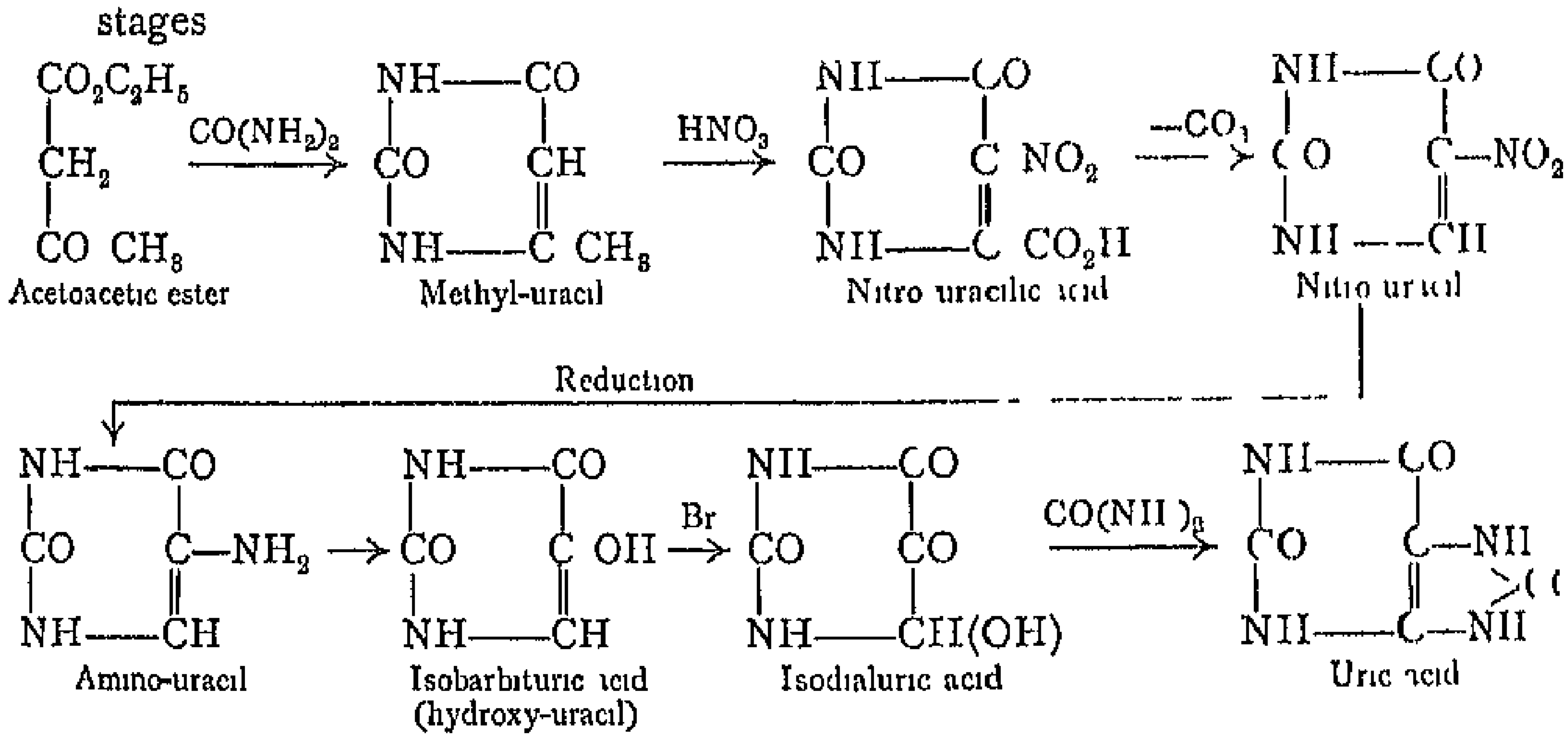


Uric acid Purone

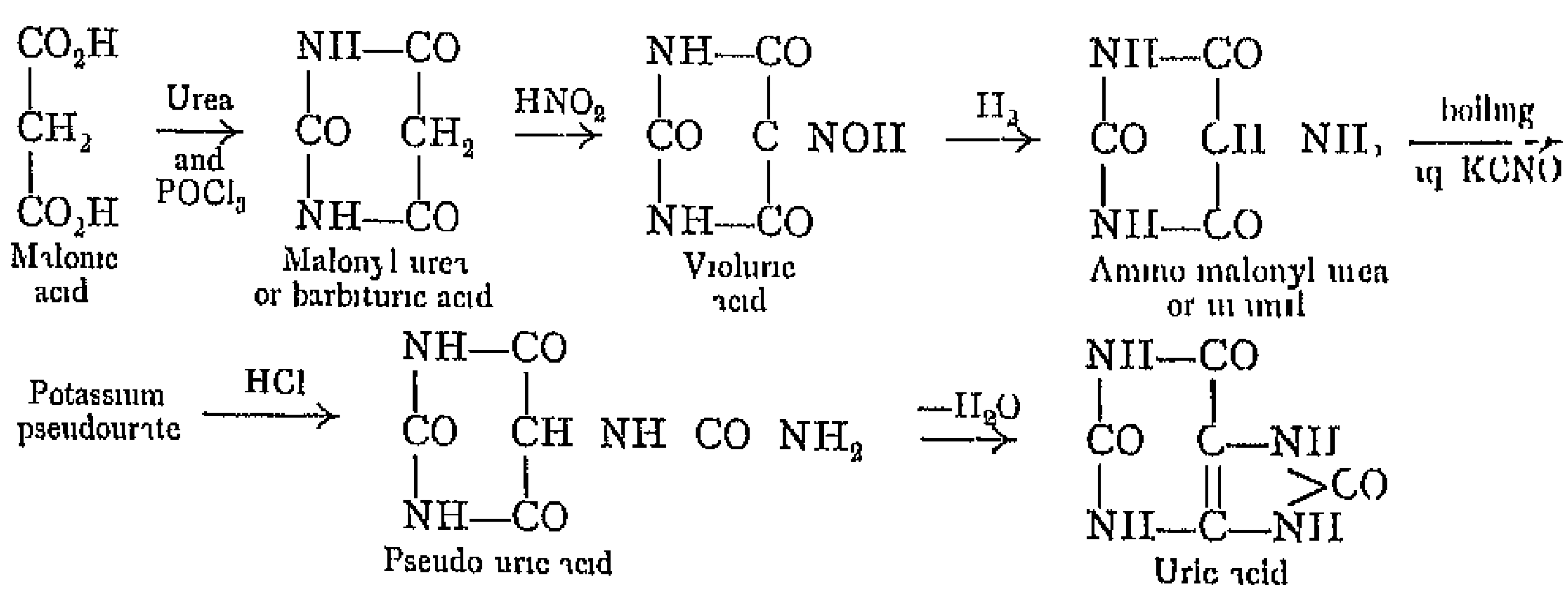
[1] E Fischer, *Ann*, 175, 243 [2] E Fischer, *Ber*, 1899, 32, 445 [3] Tafel, *Ber*, 1901, 34, 261, 1181

Acidity of the Hydrogen Atoms in Uric Acid.—It has been established[1] that the hydrogen atom in position 3 is the most strongly acidic. Its replacement by metals leads to the formation of acid salts. The atom in position 9 is next in acidic strength, and neutral urates are formed by replacement of these two atoms.

Synthesis of Uric Acid.—1. The first decisive synthesis of uric acid was accomplished in 1889 by Behrend and Roosen,[2] in the following stages:



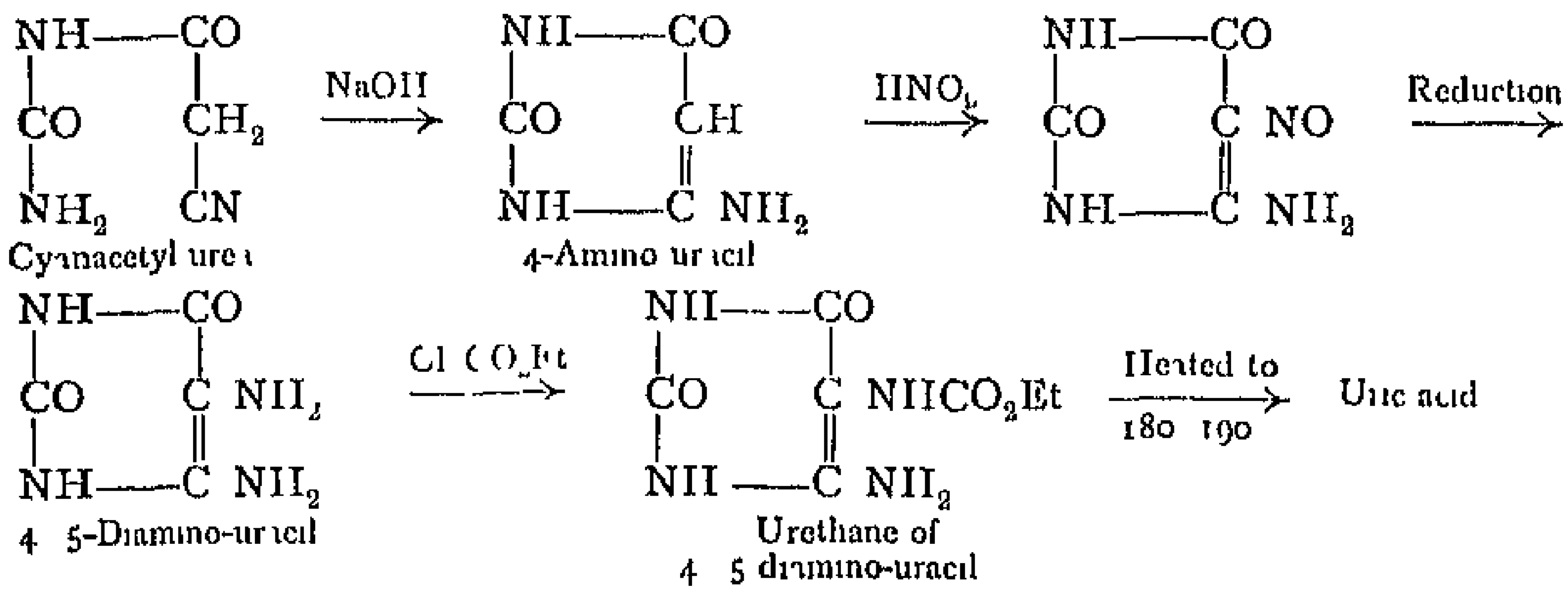
2. The next and simplest synthesis of uric acid was carried out by Fischer and Ach in 1895.[3] This depends on the removal of the elements of water from pseudo-uric acid by fusion with oxalic acid, or more conveniently by boiling with strong hydrochloric acid. Pseudo-uric acid was prepared from malonic acid in the following manner:



As violuric acid is the oxime of alloxan, this synthesis permits the reconstruction of the uric acid molecule from its chief oxidation product, alloxan. Further, by starting from methyl alloxan and dimethyl alloxan there can be obtained methyl pseudo-uric acids, from which it is possible to prepare methylated uric acids.

[1] Biltz and Herrmann, *Ber.*, 1921, 54, 1676. [2] *Ann.*, 1889, 251, 235. [3] *Ber.*, 1895, 28, 2173.

3 A synthesis of general application and hence of great preparative value is that due to Traube It makes use of cyanacetyl urea,[1] formed by condensing cyanacetic acid with urea



By utilising the alkyl derivatives of urea this synthesis may be employed for the preparation of alkylated uric acids

A compound very closely related to uric acid is **xanthine**, or 2 6 *dihydroxy-purine* (formula p 339), which may be obtained synthetically by Fischer's[2] method from 2 6 8-trichloro-purine, or by Traube's method,[3] from cyanacetyl-urea Trichloro-purine on treatment with sodium ethoxide is converted into 2 6-diethoxy-8-chloro-purine, and this with hydriodic acid yields xanthine, the ethoxy groups undergoing hydrolysis and chlorine being replaced by hydrogen Xanthine is a normal constituent of many animal tissues It is an amorphous powder which is very sparingly soluble in water On electrolytic reduction it yields *desoxy-xanthine*,[4]

$$C_5H_4O_2N_4 + 4H = C_5H_6ON_4 + H_2O$$

The most important of the five naturally occurring methyl derivatives[5] of xanthine is **caffeine**, 1 3 7-*trimethyl*-2 6 *dihydroxy-purine* (formula p 339)

It occurs in the leaves and beans of the coffee tree (1 2 per cent), in tea (2 to 4 per cent), and in kola nuts (3 per cent) It also occurs in small amount in

[1] W Traube, *Ber*, 1900, 33, 3035 [2] *Ber*, 1897, 30, 2235, *Ber*, 1899, 32, 468 [3] *Ber*, 1900, 33, 3035, *Ann*, 1904, 331, 64 For the preparation of xanthine, see H Biltz and A Beck, *J prakt Chem*, 1928, [2], 118, 166 [4] Tafel and Ach, *Ber*, 1901, 34, 1165 [5] Substituent methyl groups exert a very considerable influence on the properties of purine derivatives In general, the entrance of methyl groups increases the solubility in water and lowers the melting-point This is well illustrated by the differences in solubility shown by xanthine, theobromine and caffeine Further, the volatility (ease of sublimation) is also increased by methylation Methyl derivatives usually crystallise better than the parent compounds, and are therefore sometimes of value in identifying the latter The transformation of pseudo uric acid into uric acid is effected more readily with the methyl derivatives, and is specially promoted by the introduction of a methyl group into the 7 position Finally, the fission of the purine nucleus is influenced to a marked degree by methylation, and takes place far more readily in the case of those derivatives in which the acidic hydrogen has been totally replaced by alkyl groups

cocoa It crystallises in silky needles containing 1 molecule of water, which is partly lost in air at ordinary temperatures and completely driven off at 100° Caffeine melts at 234 5°, and on electrolytic reduction is converted into desoxy caffeine [1]

Caffeine is the component of tea and coffee responsible for the stimulating action of these beverages on the nerves and heart For this reason it is employed in medicine

Originally the bulk of the caffeine used was prepared from tea dust Nowadays it is prepared by other methods, *e g* from uric acid

Caffeine from Uric Acid—When uric acid is shaken in aqueous alkaline solution with methyl iodide, its four hydrogen atoms are replaced by four methyl groups, with the production of tetra methyl uric acid This on being heated with phosphorus oxychloride yields chloro-caffeine, in which reaction the methyl group in position 9 becomes detached, and the oxygen in position 8 replaced by chlorine Finally the chloro-caffeine is reduced to caffeine [2] An industrial process for the manufacture of caffeine takes place in the following stages Uric acid ⟶ 8 methyl-xanthine ⟶ 1 3 7 8-tetramethyl-xanthine ⟶ 1 3 7-trimethyl-8-trichloromethyl-xanthine ⟶ caffeine

For a synthesis of caffeine from cyanacetyl chloride and dimethyl urea, see W Traube, *Ber*, 1900, 33, 3035, *Ann*, 1904, 331, 46

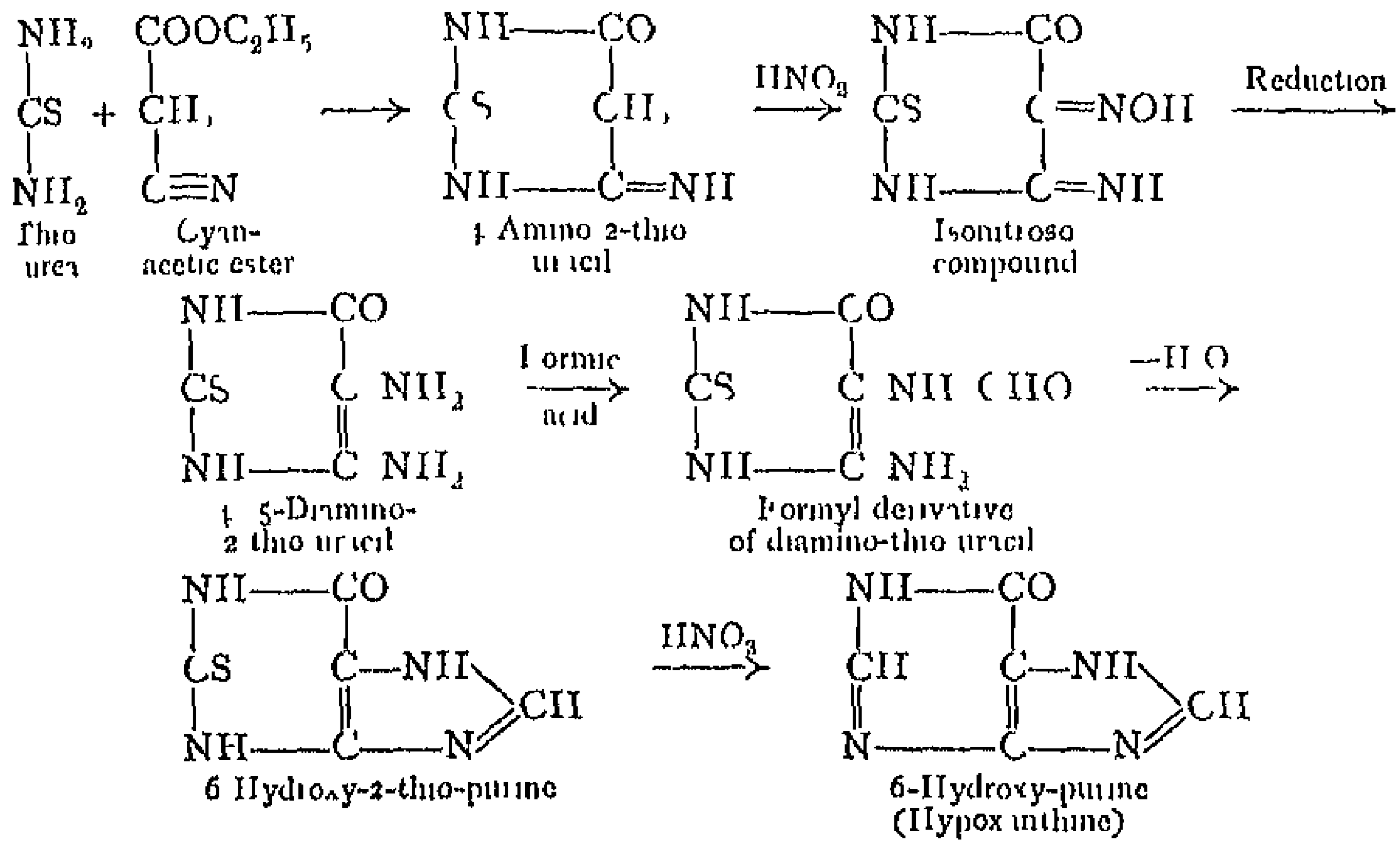
A compound closely related to caffeine is **theobromine**, 3 *7-dimethyl-2 6-dihydroxy-purine* (formula p 339), which occurs in cocoa (1 to 2 per cent) It is a white crystalline powder which sublimes unchanged at about 290° and is employed as a diuretic Its structure has been shown by synthesis from 3 7-dimethyl-uric acid [3]

Theophylline, 1 *3-dimethyl-2 6 dihydroxy-purine* (formula p 339) is isomeric with theobromine and has been found in tea The anhydrous compound melts at 264°, and in its diuretic action surpasses theobromine It was the first xanthine derivative to be prepared artificially, being obtained from 1 3-dimethyl-uric acid [4] The latter compound on treatment with a mixture of phosphorus oxychloride and pentachloride gave chloro-theophylline, which was then reduced to theophylline On the technical scale it is prepared from symmetrical dimethyl urea and cyanacetic acid [5] Another industrial method of preparation is analogous to that indicated above for caffeine, with the difference that 8-trichloromethyl-caffeine (1 3 7-trimethyl-8-trichloromethyl-xanthine) is transformed by further chlorination into 1 3-dimethyl-7-chloromethyl-8-trichloromethyl-xanthine This on hydrolysis yields theophylline It is used as a diuretic

Hypoxanthine, or *sarkine*, *6-hydroxy-purine* (formula p 339), is frequently found associated with xanthine in the animal organism, and is consequently present in extract of muscle, spleen, and liver It

[1] Tafel and Baillie, *Ber*, 1899, 32, 3206 [2] E Fischer, *Ber*, 1897, 30, 3010 [3] E Fischer, *Ber*, 1897, 30, 1839 [4] Fischer and Ach, *Ber*, 1895, 28, 3135 [5] W Traube, *Ber*, 1900, 33, 3041

is a crystalline powder of basic character, which decomposes at 150° It may be prepared from 2 6 8-trichloro-purine,[1] which on being heated with alkalis yields 6-hydroxy-2 8-dichloro-purine The latter on reduction with hydriodic acid is converted into hypoxanthine It has also been synthesised from cyanacetic ester and thiourea[2] in the following stages



Whereas the hydroxy-purines, *uric acid*, *hypoxanthine*, and *xanthine* are formed in the animal organism as intermediate or final products of metabolism with a view to subsequent elimination from the system, the following amino-purines *guanine* and *adenine*, are essential constituents of the important nucleic acids and must be regarded as indispensable for the life processes of the cell

Guanine, *2-amino-6-hydroxy-purine* (formula p 339), occurs in the pancreas of certain animals and is present in large amounts in guano It may be obtained from 6-hydroxy-2 8-dichloro-purine (dichloro-hypoxanthine) by heating with alcoholic ammonia, and reducing the chloro-guanine so formed with hydriodic acid[3], it is more readily prepared from cyanacetic ester and guanidine[4] When treated with nitrous acid it is converted into 2 6-dihydroxy-purine or xanthine

Adenine, *6-amino-purine* (formula p 339), is formed together with xanthine, hypoxanthine, and guanine when *nuclein*, the chief constituent of the cell nucleus, is boiled with dilute acids It has been synthesised by the action of ammonia on trichloro-purine, and reduction of the 6-amino-2 8-dichloro-purine thus obtained[5] Like hypoxanthine, it may also be prepared from sulphur compounds,

[1] E Fischer, *Ber*, 1897, 30, 2226 [2] W Traube, *Ann*, 1904, 331, 67. [3] E Fischer, *Ber*, 1897, 30, 2251 [4] W Traube, *Ber*, 1900, 33, 1371 [5] E Fischer, *Ber*, 1897, 30, 2238

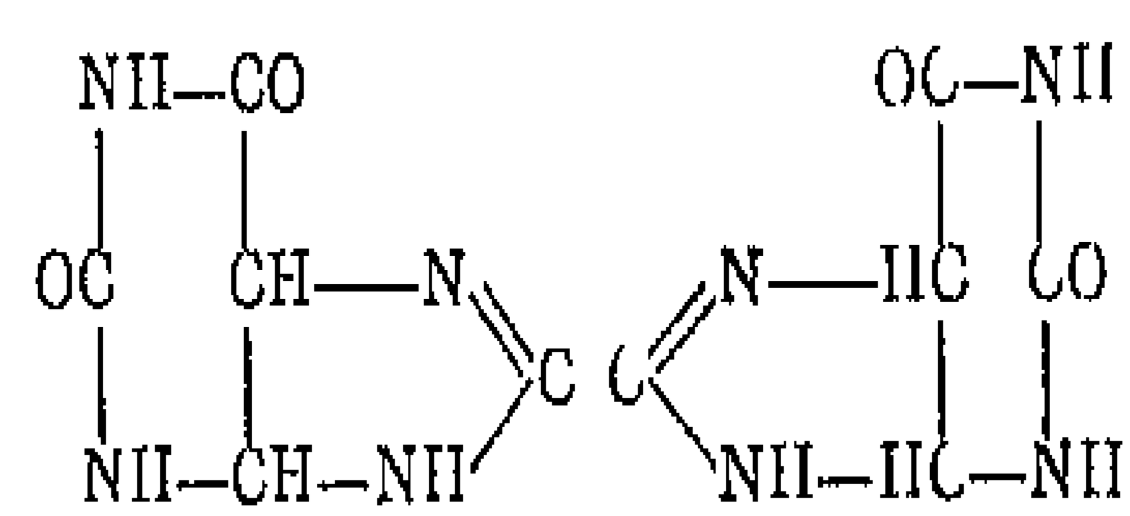
the starting materials in this case are thiourea and the nitrile of cyanacetic acid. When treated with nitrous acid, adenine is converted into 6-hydroxy-purine or hypoxanthine.

Recent investigations indicate that the colouring matters of butterflies' wings are also to be classed as purine derivatives. Wieland proposes to name these pigments *lepidopterines* or *pterines*.

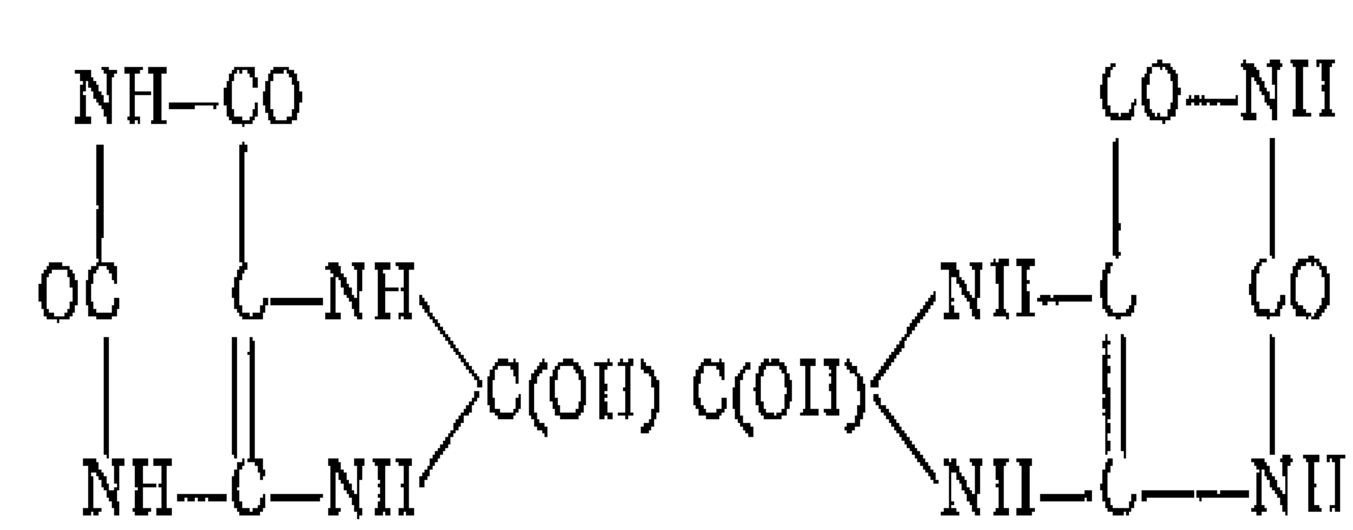
Xanthopterine,[1] $(C_5H_5O_2N_4)_2$, the yellow pigment of the lemon butterfly, *Gonepteryx rhamni*, was obtained from the ammonium salt as a yellow amorphous powder. After purification by way of the barium salt it formed orange brown globular aggregates, probably of structure I.

Leukopterine,[2] $(C_5H_5O_3N_4)$, the pigment in the wings of the white butterfly, was isolated from the sodium salt in almost colourless crystals. It bears the same relationship to uric acid, $C_5H_4O_3N_4$, as xanthopterine does to xanthine. It has been formulated as II.

I



II



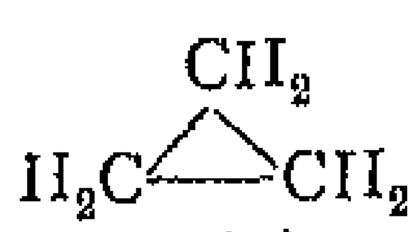
[1] H. Wieland and C. Schöpf, *Ber.*, 1925, 58, 2178. [2] C. Schöpf and H. Wieland, *Ber.*, 1926, 59, 2067.

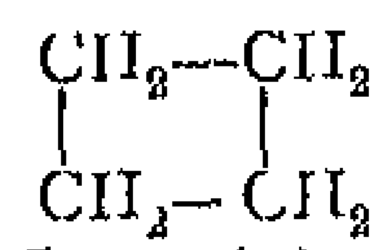
PART II

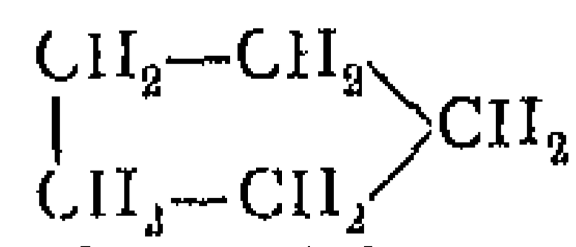
Chemistry of the Carbocyclic Compounds

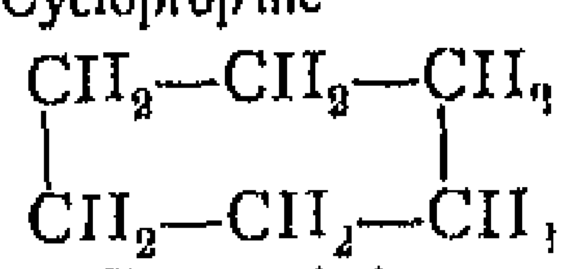
As already stated on p. 18, compounds containing open chains are classed as aliphatic, and those containing closed chains or rings as cyclic. The following section deals with those cyclic compounds in which the rings are built up entirely of carbon atoms, and which are therefore most conveniently grouped under the heading *carbocyclic*.[1]

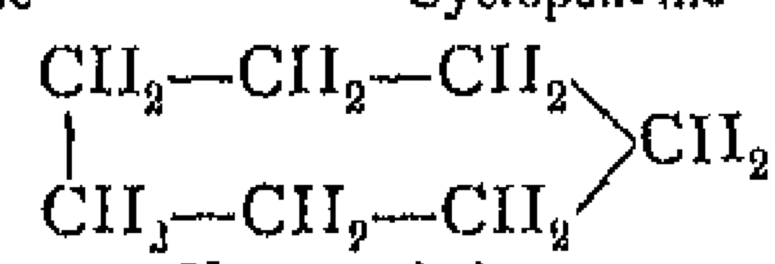
Included in this group are certain hydrocarbons having the same composition, (C_nH_{2n}), as the homologues of ethylene, although possessing very different properties. These hydrocarbons are termed polymethylenes, or, according to the Geneva nomenclature, are named by prefixing *cyclo* to the names of the corresponding normal paraffins.


Trimethylene,
Cyclopropane


Tetramethylene,
Cyclobutane


Pentamethylene,
Cyclopentane


Hexamethylene,
Cyclohexane


Heptamethylene,
Cycloheptane

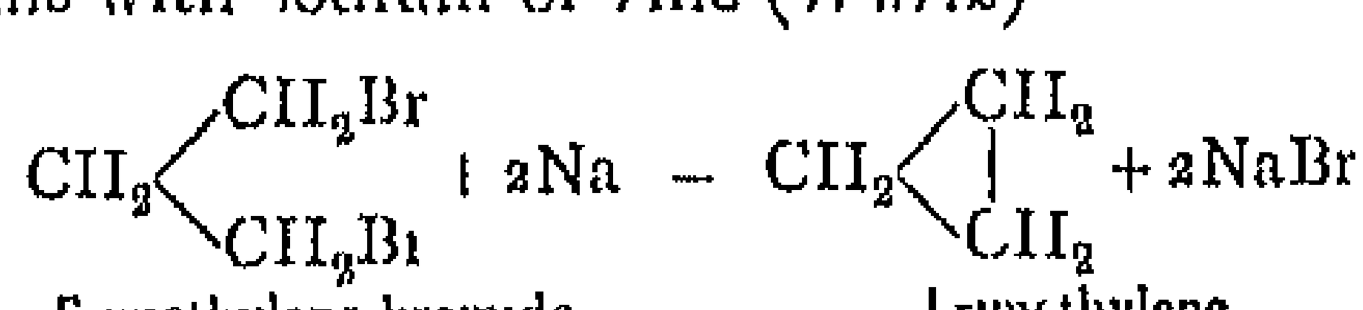
Some of these compounds give rise to large numbers of derivatives.

Of far greater interest than these hydrocarbons and their derivatives is the large and important class made up of the true aromatic compounds, which are related to benzene, C_6H_6. Before discussing the latter in detail, a brief survey of the other groups will be given.

I

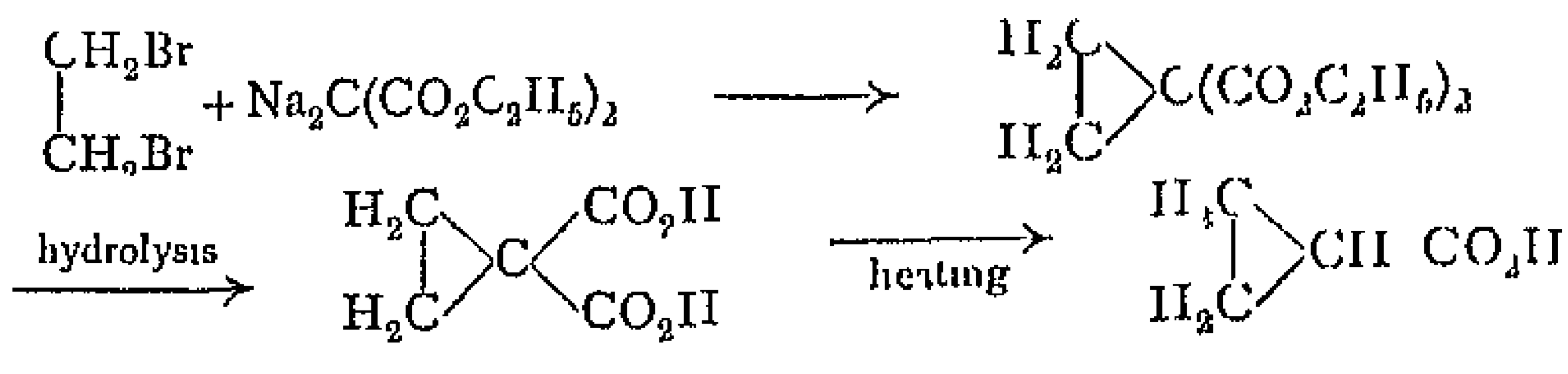
Tri-, Tetra-, Penta-, and Heptamethylene[2] Compounds and the Cyclo-olefines

The cycloparaffins may be prepared by treating the corresponding dibromo-paraffins with sodium or zinc (*Wurtz*).


Trimethylene bromide Trimethylene

[1] These are sometimes called homocyclic or isocyclic compounds. [2] Hexamethylene and its derivatives are treated later, in connection with the aromatic compounds. For a more detailed description of carbocyclic compounds reference should be made to W. H. Perkin, jun., *Ber.*, 1902, 35, 2091.

Mono- and dicarboxylic acids of tri-, tetra- and pentamethylene are produced by the action of sodio-malonic ester on ethylene, trimethylene and tetramethylene bromides respectively



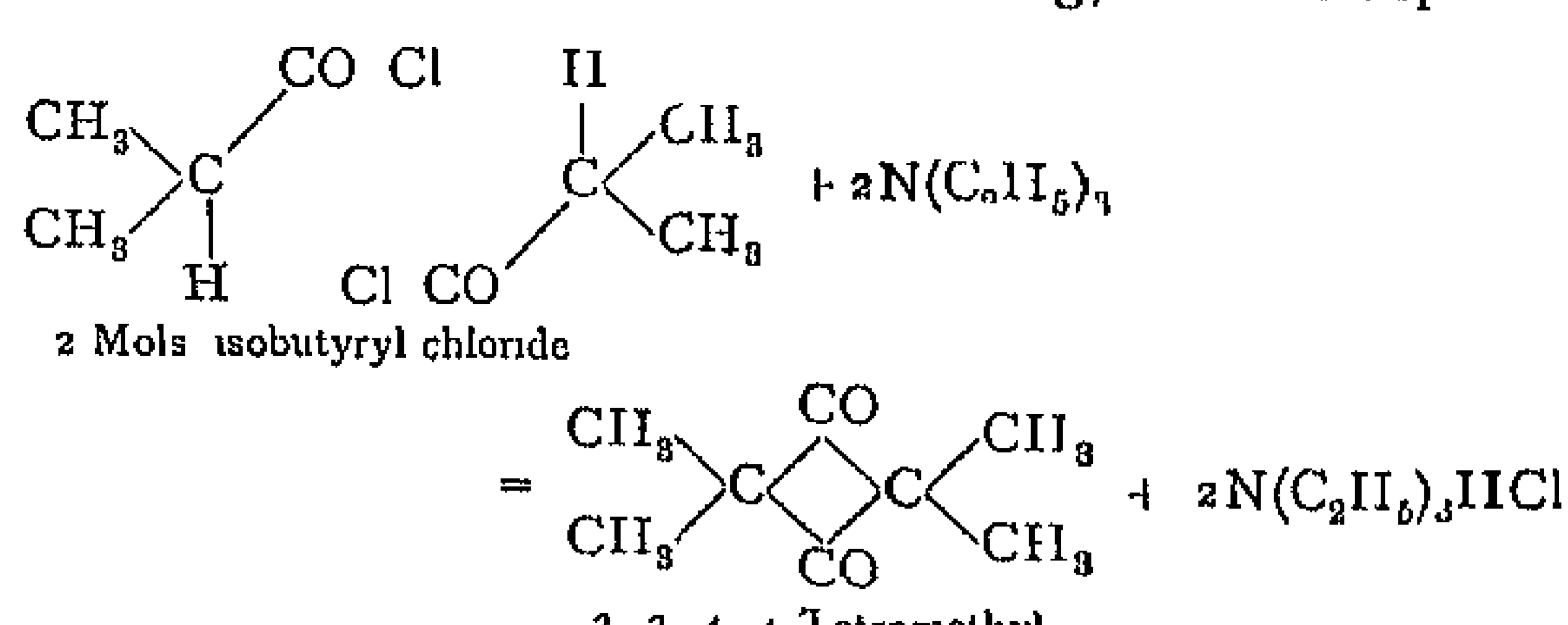
Ketones of the cycloparaffins are formed from the calcium salts of certain higher dicarboxylic acids of the fatty series by dry distillation (p 272)

Cyclobutene has been prepared by Willstatter by distilling the quaternary ammonium hydroxide of aminocyclobutane It boils at 2° (729 mm) On reducing this compound catalytically with the aid of nickel at 100°, pure cyclobutane, b p 11° to 12°, was obtained[1] If the reduction is carried out at the more usual temperature of 180° to 200°, the cyclobutane is completely reduced to butane In the following table a summary is given of the most important physical constants of the polymethylenes so far investigated

	B p	M p	d_4^0	Mol Vol at 0	Difference
Cyclopropane	approx − 35°	− 127°	—	—	
Cyclobutane	11° to 12°	liq at − 80°	0 7038	79 06	12 03
Cyclopentane	49°	liq at − 80°	0 7635	91 09	14 10
Cyclohexane	81°	6 4°	0 7934	105 19	12 81
Cycloheptane	117° to 117 5°	—	0 8252	118 00	12 92
Cyclooctane	145 3° to 148°	11 5°	0 850	130 92	28 54
Cyclononane	170° to 172°	—	0 785	159 46	

For preparation of cyclopropane in the pure state, see M Trautz and K Winkler, *J prakt Chem*, 1922, 104, 37

Among diketones of the cyclobutane series, containing ketonic oxygen attached to a carbon atom in the ring, the first representative



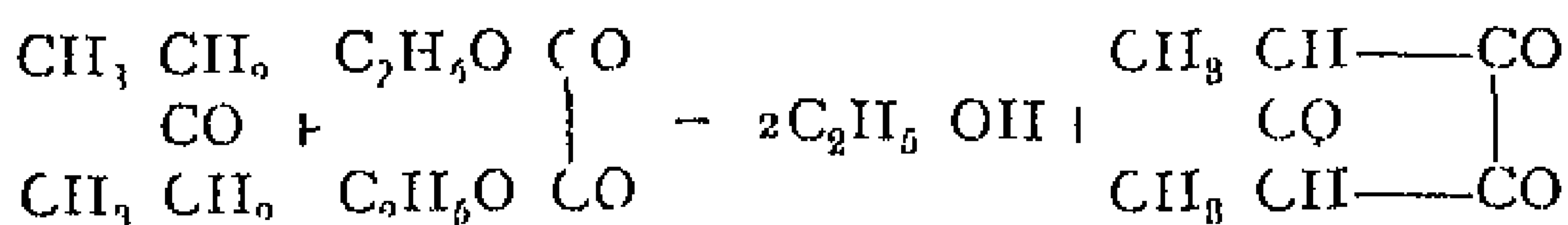
2 Mols isobutyryl chloride

2 2 4 4 Tetramethyl cyclobutan dione 1 3

[1] Willstatter and Bruce, *Ber*, 1907, 40, 3979

to be prepared was diketo-tetramethyl-cyclobutane. This was obtained by the action of triethylamine on isobutyryl chloride.[1]

Substituted acetones condense readily with oxalic ester, two molecules of alcohol being eliminated and cyclopentane-triones[2] formed:



Diethyl ketone Oxalic ester Dimethyl cyclopentane-trione

Up to the present it has not been found possible to carry out this reaction with acetone itself.

It was observed by Zelinsky[3] that when 1-methyl-3-cyclopentanone is led over nickel at 250° it is converted into methyl cyclopentane, b.p. 72° to 72.2°. This is a very convenient method for the preparation of the compound. Here, notwithstanding the comparatively high temperature and the presence of nickel as catalyst, no dehydrogenation of the pentamethylene hydrocarbon takes place, and this appears to be a characteristic distinction between the five- and six-membered rings.

In spite of the similarity in structure between the cyclo-paraffins and their derivatives and true aromatic compounds, these two series show very considerable differences in chemical behaviour, the former approximating in properties to the aliphatic series. Following a suggestion of Bamberger, those compounds combining the aromatic ring structure with the character of aliphatic substances are sometimes known as aliphatic-cyclic or *alicyclic compounds*.

On examining the physical properties of saturated compounds containing closed chains, it is seen that these possess higher boiling-points and higher specific gravities than the isomeric unsaturated aliphatic compounds, and also than the saturated aliphatic compounds containing an additional two atoms of hydrogen. This may be illustrated by the following figures: cyclohexane, C_6H_{12}, b.p. 81°; *n*-hexane, C_6H_{14}, b.p. 69°; *n*-hexylene-1, C_6H_{12}, b.p. 68°. Considerable differences are also visible on comparing the magnetic rotation of saturated ring compounds with that of the corresponding unsaturated compounds having open chains. Thus the magnetic rotation of hexamethylene, C_6H_{12}, is 5.664, and that of hexylene or methylpropylethylene, C_6H_{12} is 7.473.

The Relative Stability and Ease of Formation of Ring Compounds (Baeyer's Strain Theory)

A striking point which emerges from a closer examination of the above-mentioned ring systems is the difference in their stability and in

[1] Wedekind, *Ber.*, 1906, 39, 1631; 1911, 44, 3285. For the formation and rupture of four membered rings see also Staudinger, *Ber.*, 1911, 44, 521. [2] Claisen and Ewan, *Ann.*, 1894, 284, 247. Diels, *Ber.*, 1906, 39, 1328. [3] Zelinsky, *Ber.*, 1911, 44, 2781; 1926, 59, 2580.

the relative ease with which they are formed. Baeyer explained this in his "strain theory" as follows:—

According to the fundamental hypothesis of stereochemistry, the four affinities of a carbon atom act in the direction of lines which may be imagined to be drawn from the central point of a tetrahedron to its summits, and thus make an angle of 109° 28′ with each other. If, however, carbon atoms unite together to form a closed chain these affinities become diverted from their natural directions, and a strain is set up which may be measured by the angle of displacement. As may easily be seen, this tension is least in the five-membered ring. Rings possessing a smaller or greater number of carbon atoms than the pentamethylene ring are under greater tension than the latter. The magnitude of the tension in any individual case is readily calculated. In the trimethylene ring, for example, the carbon atoms may be imagined to be at the corners of an equilateral triangle; the bonds joining them thus enclose angles of 60°. The distortion of each bond is therefore $\frac{1}{2}$ (109° 28′ − 60°) = 24° 44′. The following summary gives the values for the distortion in the formation of different polymethylene rings.

(Double bond)	Tri-	Tetra-	Penta-	Hexa-	Hepta-
+54° 44′	+24° 44′	+9° 34′	+0° 44′	5° 16′	9° 33′

From these figures it follows that the pentamethylene ring is under the least strain and should therefore be the most stable. In the remaining systems, on the other hand, the valency bonds tend, in varying degree, to assume their original positions in space and therefore to open up the ring. In the case of the above rings these theoretical deductions have been largely confirmed by experiment. In ethylene the strain is greatest, and hence the tendency to form addition compounds with the simultaneous opening of the ring is at its highest. This shows itself in the extraordinary speed with which ethylene adds on chlorine, bromine, or hydrobromic acid. The distortion is far less in the case of trimethylene, and consequently the opening of the ring by addition of bromine or hydrobromic acid is effected much less readily than in the case of ethylene. The tetramethylene ring, again, is more stable than the trimethylene ring, as is readily seen on comparing certain derivatives of these two hydrocarbons. Trimethylene carboxylic acid, for example, is easily attacked by hydrobromic acid, whereas tetramethylene carboxylic acid under the same conditions is scarcely affected. Finally, pentamethylene and hexamethylene carboxylic acids are unchanged even on prolonged boiling with hydrobromic acid.

Further confirmation of the validity of the strain theory is also found in the heats of combustion of compounds containing saturated 3-, 4-, 5- and 6-carbon rings.[1]

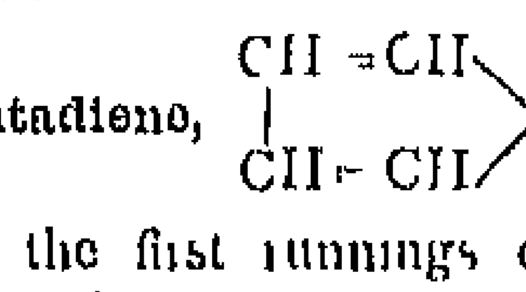
[1] *J. pr. Ch.*, 1892, [2], 46, 489. See, however, Ingold, *J. C. S.*, 1921, 119, 305.

An interesting development of stereochemical theory may often be observed in the properties of a homologous series, *i.e.* of a series of compounds containing a *growing chain*. When the latter contains 5 or 6 carbon atoms (or 10, 11, etc.) the properties of the corresponding compounds often deviate from those of the preceding and succeeding members of the series. This is due to the fact that a chain of this length will tend to return on itself, thus subjecting a group in the neighbourhood of atom 1 to an abnormal influence. Such abnormalities have been noted in connection with optical activity (Frankland, Pickard and Kenyon), acid strength and various other properties. *Hexyl resorcinol* (caprokol), for example, has been found to be the most effective internal antiseptic out of a number of homologous derivatives (see p. 418).

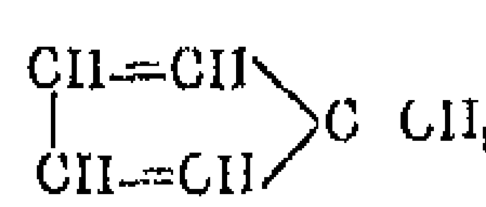
As has recently been shown by Ruzicka, the conditions may be quite otherwise in the case of rings containing a large number of carbon atoms. Although not readily prepared, such compounds possess a high degree of stability, and it appears that, by virtue of its magnitude, the ring is able to crumple up or twist itself into positions in which there is little or no distortion of the carbon bonds and hence no strain. Naturally occurring substances of this type are the strongly odorous ketones *muscone* and *civetone*, having 15 and 17 membered rings respectively (see p. 352).[1]

CYCLO-OLEFINES

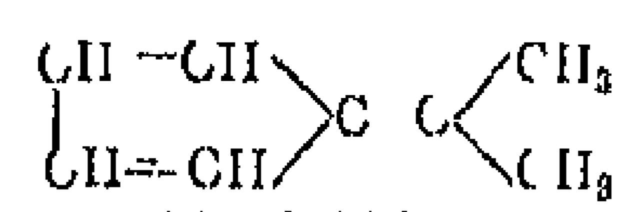
The cyclo olefines bear the same relationship to the cycloparaffins as the olefines to the paraffins.

Cyclopentadiene,  is a colourless liquid, b.p. 41°, which is obtained in the first runnings of the crude benzene from coal tar. It readily polymerises, and at temperatures up to 100° yields chiefly dicyclopentadiene, $C_{10}H_{12}$. Above this, *e.g.* at 135°, polycyclopentadienes $(C_5H_6)_n$ are also formed.

In cyclopentadiene the two hydrogen atoms of the CH_2 group are very reactive, owing to the proximity of the two double bonds; one of them, for example, may be replaced by potassium. Further, under the influence of sodium hydroxide or ethoxide, cyclopentadiene condenses with aldehydes and ketones, the CH_2 group of the former reacting with the C : O group of the latter with elimination of water. The resulting condensation products, of which that with acetone possesses the structure II, have an intense orange to blood red colour, and may be represented as substitution products of an isomeride of benzene having the formula I. Thiele calls this unknown hydrocarbon fulvene.

I 

Fulvene

II 

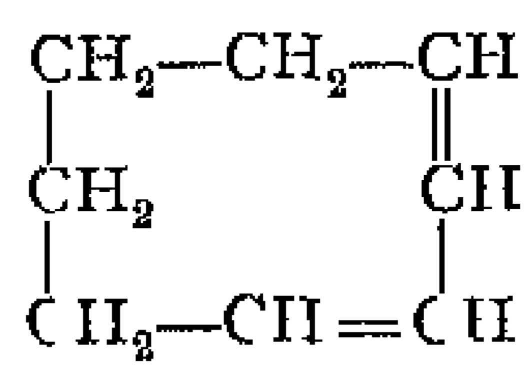
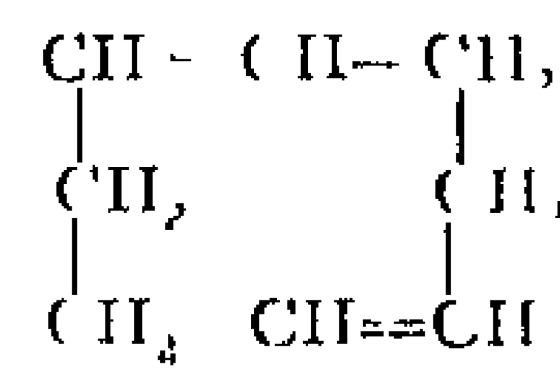
Dimethyl fulvene

The fulvenes provide an interesting illustration of the manner in which the colour of an organic compound is influenced by the presence and arrangement of double bonds within the molecule.[2]

[1] Ruzicka, *Helv. chim. Acta*, 1926, 9, 339. [2] See also *Ber.*, 1900, 33, 668.

Cycloheptatriene, *tropilidene*, $\begin{matrix} CH\ CH\ CH \\ \| \\ CH\ CH\ CH \end{matrix}\!\!>\!CH_2$, is a degradation product of the alkaloids cocaine and atropine, and can be prepared from suberone[1] It is a liquid, b p 116°, which smells of leeks

Cyclo octadiene (I) has been obtained by the exhaustive methylation (see p 647) of pseudo pelletierine,[2] an alkaloid found in pomegranate

I  II 

It boils at 39 5° under 16 5 mm pressure, and possesses a penetrating and nauseous smell It polymerises very readily (explosively on heating) to yield dicyclo octadiene When the dihydrobromide of cyclo octadiene is heated with alkalis or quinoline, hydrobromic acid is removed and another unsaturated hydrocarbon of the formula C_8H_{12} is produced This boils at 143° to 144°, and perhaps corresponds to formula II Whereas compound I is highly unstable and readily polymerises, the isomeric compound II is very stable The latter is easily reduced to cyclo octane by the Sabatier and Senderens method

Cyclo octanone is an example of a cyclo octane derivative It is formed in small amounts (5 per cent) when the calcium salt of azelaic acid is distilled According to Ruzicka,[3] yields of 25 per cent may be obtained by distilling the thorium salt

Cyclo nonanone is obtained in small yield by the dry distillation of thorium sebacate It boils at 95° to 97° under a pressure of 17 to 18 mm When reduced in boiling alcoholic solution with metallic sodium it yields cyclo nonane (See table on p 348)

Monocyclic ketones containing 16, 18 and 30 carbon atoms respectively in the ring have also been synthesised[4]

Naturally occurring compounds of this type are the powerfully odorous ketones **muscone** (from the musk deer) and **civetone** (from the civet cat) **Muscone,** $C_{16}H_{30}O$, is a saturated optically active liquid, which has been shown by Ruzicka to contain a 15 membered ring **Civetone,** $C_{17}H_{30}O$, melts at 31° It is a symmetrical unsaturated ketone of the formula $\begin{matrix} CH\ (CH_2)_7 \\ \| \\ CH\ (CH_2)_7 \end{matrix}\!\!>\!CO$, which yields azelaic acid on oxidation

RUBBER[5]

Rubber is obtained from the sap of a number of trees belonging to the *Apocynaceæ*, *Moraceæ*, and *Euphorbiaceæ* families These are found in tropical countries, particularly in South America, Africa and the

[1] Willstätter, *Ann*, 1901, **317**, 204 [2] Willstätter and Veraguth, *Ber*, 1907, **40**, 957 Willstätter and Waser, *Ber*, 1911, **44**, 3423 For cyclo octadiene, see also Dobner, *Ber*, 1907, **40**, 146 [3] *Helv chim Acta*, 1926, **9**, 339, *et seq* [4] *Helv chim Acta*, 1928, **11**, 496 [5] See *Chemistry of Rubber*, by B D N Luff (Benn, 1923) C D Harries, *Untersuchungen über die natürlichen und künstlichen Kautschukarten* (Berlin, 1919)

East Indies. A very valuable rubber tree is the *Ficus elastica*. The bark of the tree is "tapped" by making a small incision and the milky *latex* which oozes out is collected in pans. The latex is next polymerised, *e.g.* by subjecting it to the action of smoke, to give crude rubber. This is freed from admixed sand, bark and other impurities by boiling with water, when the mass becomes plastic. It is then kneaded between warm rollers until homogeneous, and finally rolled out into sheets. The product so obtained consists essentially of **caoutchouc**, the hydrocarbon constituent of rubber. It is insoluble in water, dilute acids and alkalis, but soluble in benzene, carbon disulphide and chloroform. On dry distillation it yields isoprene (p. 115). With N_2O_3 the various forms of caoutchouc are generally converted quantitatively into a nitrosite of the composition $(C_{10}H_{15}N_3O_7)_2$, a reaction which may be used technically for the quantitative estimation[1] of rubber in rubber goods.

Caoutchouc is remarkable for its great elasticity, but it gradually loses this valuable property with rise of temperature and when cooled becomes hard. This defect may be partly overcome by treating the rubber with sulphur (*vulcanisation*), which also increases its resistance to chemical reagents. In this process the caoutchouc is heated with sulphur to 140°, or treated with a mixture of carbon disulphide and sulphur chloride. In the former case "fillers" and pigments such as antimony sulphide and zinc sulphide may also be added. When a larger proportion (25 to 40 per cent.) of sulphur is employed, *ebonite* or hard rubber is obtained.

Distillation of Caoutchouc[2].—When subjected to dry distillation rubber decomposes to give a mixture of products, the more volatile of which boil as low as 25°, whilst others range above 300°. Of these products only two fractions have been carefully investigated, namely those boiling at 30° to 40° and 160° to 170° respectively. In the latter fraction is found *dipentene* (Wallach), and in the former *isoprene*, *dimethyl-allene* and *dihydro-isoprene*. This problem has been very largely cleared up by the work of Ipatieff, who also showed that isoprene could only be prepared in the pure state by indirect methods. The constitution of isoprene has been established by the syntheses of Euler and Ipatieff. Harries found that from 1500 gms. of good caoutchouc only 35 gms. of isoprene boiling at 33° to 34° could be obtained.

Synthesis of Caoutchouc.—The first real synthesis of caoutchouc is due to Tilden in 1892, who discovered that a sample of isoprene, prepared by heating dipentene, had in the course of time polymerised into rubber. The technical application of this polymerisation was discovered independently by Matthews[3] and Harries[4] in 1910.

[1] Harries, *Ber.*, 1901, 34, 2991; 1902, 35, 3256, 4429; 1903, 36, 1937; 1905, 38, 87.
[2] R. Willstätter, *Ber.*, 1911, 44, 3423.
[3] See Perkin, *J. S. C. I.*, 1912, 31, 616; Strange and Graham, Eng. Pat. 24790, 1910.
[4] Harries, *Ann.*, 1911, 383, 184.

The best results are obtained by the use of pure isoprene, which on warming for about 50 hours to 60° with sodium wire in a sealed tube is practically quantitatively converted into a solid rubber. Harries showed that the polymerisation could also be effected, though less satisfactorily, by heating isoprene with glacial acetic acid to a temperature above 100° in a sealed tube.

By the above method it is possible to convert many hydrocarbons containing conjugated double bonds into rubber-like products. Industrial methods of preparing isoprene and analogous hydrocarbons therefore possess a very great interest. The manufacture of caoutchouc from acetone and aluminium as starting materials may be carried through in the following manner.

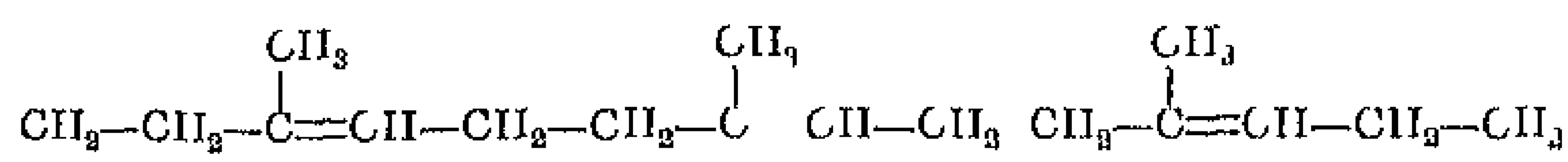
When acetone is treated in warm benzene solution with very thin aluminium foil, a compound of aluminium and pinacol is formed together with a small amount of isopropyl alcohol, which is isolated during the recovery of unchanged acetone. The compound is decomposed by warm aqueous alkali to give pinacol and aluminium hydroxide, after which the pinacol is isolated by fractionation and purified by crystallisation from water and redistillation. It is then heated with a catalyst (*e.g.* Al_2O_3 at 400°), when it decomposes into *dimethyl-butadiene*, pinacolone and water. The dimethyl-butadiene is separated from admixed products by fractional distillation, and is converted by polymerisation at moderate temperatures into methyl-caoutchouc H, or at higher temperatures into methyl caoutchouc W. These two varieties are then further worked up in a rubber factory. Like the natural product, the methyl-caoutchoucs can be mixed with sulphur and fillings and vulcanised for the production of rubber goods.

$$\underset{\text{Acetone}}{(CH_3)_2CO} \longrightarrow \underset{\text{Pinacol}}{(CH_3)_2C(OH)\cdot C(OH)(CH_3)_2} \longrightarrow \underset{\text{Dimethyl-butadiene}}{CH_3\cdot\overset{H_2C}{\overset{\|}{C}}—\overset{CH_2}{\overset{\|}{C}}\cdot CH_3} \longrightarrow \underset{\text{Methyl-caoutchouc}}{(C_{12}H_{20})_x}$$

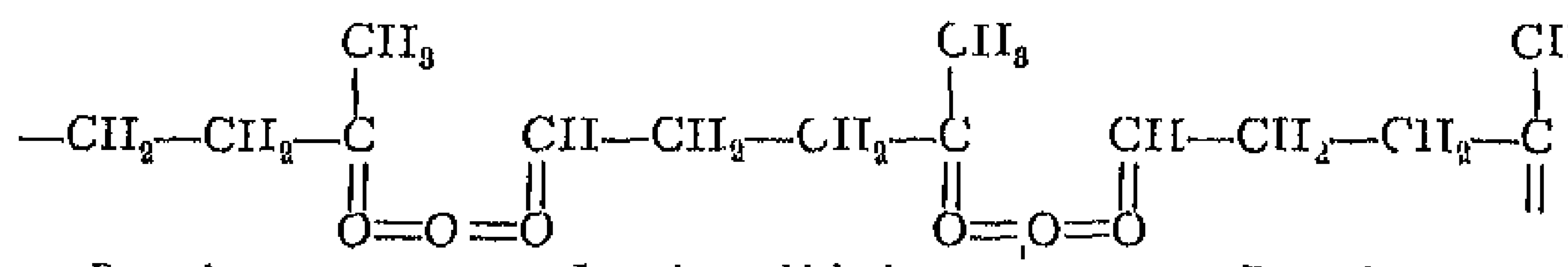
Constitution of Caoutchouc.—Caoutchouc is a hydrocarbon of the empirical formula C_5H_8. It is optically inactive and probably does not contain an asymmetric carbon atom. Pummerer and co-workers[1] have attempted to determine the molecular weight in menthol and in camphor solution, using the cryoscopic method. Their results indicate $(C_5H_8)_n$, where $n = 16$ to 24. On bromination the so-called tetrabromide of the formula $C_{10}H_{16}Br_4$ is produced. This suggests that there is one ethylenic linkage for every C_5H_8 in the molecule, a suggestion also borne out by the formation of an ozonide of the formula $(C_5H_8O_3)_n$, when ozone is passed into a chloroform solution of the hydrocarbon. The ozonide is readily soluble, and when boiled with water is decomposed into lævulinic acid, lævulinic aldehyde, and lævulinic aldehyde peroxide. From determinations of the molecular weight of this ozonide and its

[1] See *Ber.*, 1929, 62, 2628.

ease of decomposition, Harries showed that caoutchouc is depolymerised by the action of ozone, but his earlier conclusion than an 8-carbon ring is the basis of the caoutchouc molecule has proved to be untenable[1] A later suggestion of Harries is that the ring is composed of a small number of isoprene units (*e g* five) Pickles[2] has proposed a closed chain structure built up of an indeterminate number of C_5H_8 molecules, and formulated as follows —



Polymerisation is here represented as being purely chemical in nature, the union of isoprene molecules being accompanied by a rearrangement of the double bonds The ozonide is assumed to be formed as a result of the separation of the carbon atoms at the points originally occupied by the double bonds, with the production of a compound having as its basis the following structure



Peroxide Lævulinic aldehyde Peroxide.

Water brings about decomposition of the ozonide at the points shown, with the formation of lævulinic aldehyde, lævulinic aldehyde peroxide, and also lævulinic acid as a further oxidation product of the aldehyde

Staudinger,[3] who advocates an open chain structure of the above formula, has hydrogenated caoutchouc at 270° under 100 atmospheres pressure in the presence of platinum as catalyst The *hydrocaoutchouc* so obtained was found to decompose in a high vacuum at 350-390°, giving a quantitative yield of products having the formula $(C_5H_{10})_n$ Pummerer and Burkard[4] hydrogenated caoutchouc under much milder conditions in hexahydrotoluene solution Two atoms of hydrogen were absorbed for every eight already present, but the hydrocaoutchouc thus prepared differed in its properties from that of Staudinger. As yet no explanation can be advanced for these differences

Staudinger[5] succeeded in preparing a *caoutchouc hydrobromide* (bromo-hydrocaoutchouc) at ordinary temperatures, which also proved to be a colloid On treatment with zinc alkyls this gave small yields of impure *methyl-* and *ethyl-hydrocaoutchoucs*, having properties similar to those of hydrocaoutchouc

It will thus be seen that the evidence bearing on the constitution of rubber is extremely difficult to interpret At the present time it

[1] Harries and Fonrobert, *Ann*, 1914, 406, 173 Harries and Evers, *J C S*, 1922, 122, A, i, 357 [2] *J C S*, 1910, 97, 1085 [3] *Ber*, 1924, 57, 1203, 1929, 468, 1 [4] *Ber*, 1922, 55, 3458, Pummerer and Koch, *Ann*, 1924, 438, 294 [5] H Staudinger and V Widmer, *Helv chim Acta*, 1924, 7, 842

seems very questionable whether caoutchouc is an individual substance[1], the indications rather point to its being a mixture of closely related compounds These compounds, whether built up of small cyclic units as assumed by Harries, or of large chains closed or open, as suggested by Pickles and Staudinger respectively, appear to bear a definite relationship to the terpene group

Guttapercha strongly resembles rubber and is prepared from the sap of certain plants (Sapotaceae) found in Malacca and the East Indies It is purified in a similar manner to rubber, and is extensively used for making moulds, as insulating material, etc

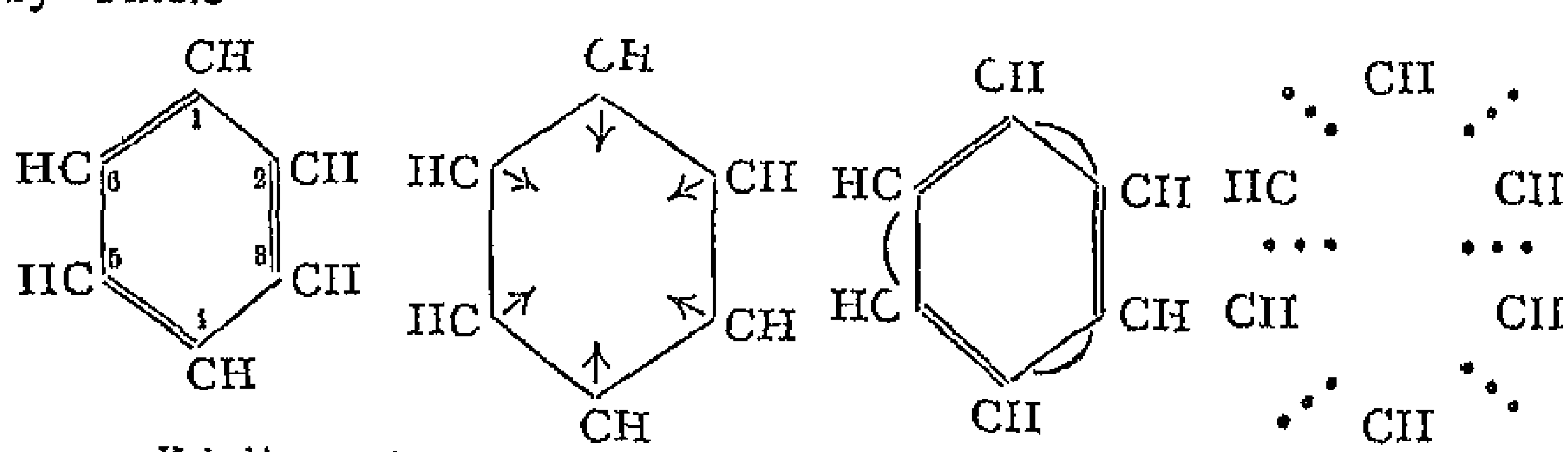
II

Introduction to the Aromatic Series

CONSTITUTION OF BENZENE

A very large number of compounds is derived from the hydrocarbon benzene, C_6H_6, many of which are of great importance industrially Certain of these substances were obtained originally from aromatic oils and resins, and as they were of unknown constitution and possessed a pleasant odour, they were classed together as *aromatic compounds* This term is now reserved for benzene derivatives

The problem of the constitution of benzene was attacked many years ago by Kekulé and has not yet been finally solved Three formulæ come into serious consideration, namely, that of Kekulé, the centric formula of Armstrong and Bamberger, and that proposed by Thiele



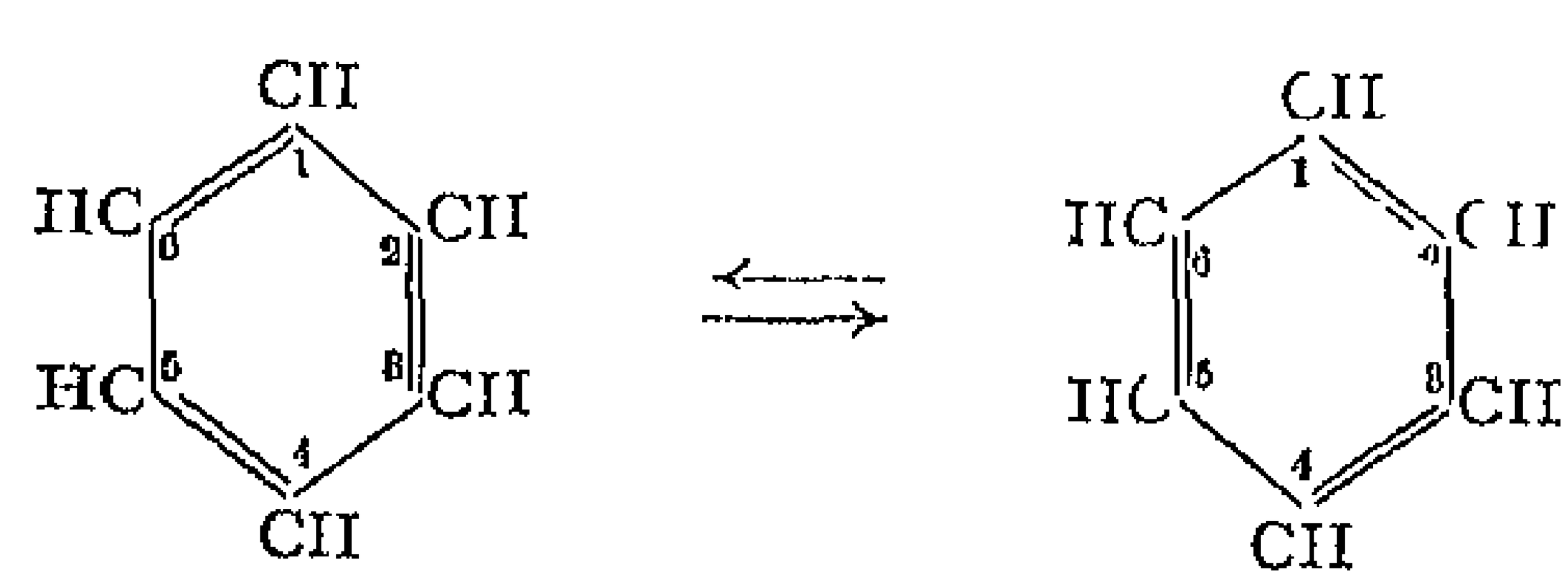
Kekulé Armstrong and Bamberger Thiele Electronic formula[2]

In proposing his formula for benzene, Kekulé[3] was guided by two regularities already established in connection with the chemistry of aromatic substances Each benzene compound derived from the hydrocarbon by the replacement of one atom of hydrogen by

[1] Compare R Pummerer, *Ber*, 1927, 60, 2148, 2152, 2163 [2] For an alternative see p 29
[3] Kekulé, *Ann*, 1866, 137, 129

another atom or radical existed in one form only. On the other hand, each di-substitution product of benzene occurred in three isomeric forms. From the first of these statements it followed that the six hydrogen atoms of benzene are chemically equivalent to one another, as was later shown conclusively by Ladenburg.[1] Accordingly, the benzene formula should have each of the six hydrogen atoms attached in a similar manner to carbon, a condition which is fulfilled by the formulæ $C_4(CH_3)_2$, $C_3(CH_2)_3$, and $(CH)_6$. Of these, however, only the last satisfies the second condition, that three isomeric di-substitution products should be possible. Hence Kekulé came to the conclusion that benzene must contain a closed chain of six carbon atoms, to each of which is attached one hydrogen atom. A doubtful point in this formula is the position of the fourth valency of the carbon atoms. Kekulé suggested that each carbon was linked to one of its two neighbours by a double bond, thus arriving at the above formula for benzene.

Kekulé's formula, however, does not satisfy all the requirements. It was first pointed out by Ladenburg that the existence of four structurally isomeric di-substitution products would be expected from a configuration of this kind, whereas, as already mentioned, the observed number is always three. In addition to the three di-derivatives represented by the positions 1 : 2, 1 : 3, and 1 : 4, there would be expected, according to the Kekulé formula, a fourth isomer of the type 1 : 6, since this differs from the 1 : 2 position in the arrangement of the double bond. By means of a further hypothesis Kekulé was able to bring his formula into harmony with the experimental facts. The atoms within the molecule are represented as being in a constant state of vibration between certain positions of equilibrium, so that directly linked atoms strike one against another, and in unit time each atom receives as many impacts as would correspond to its valency. In the special case of benzene, a carbon atom alternately makes one and two contacts per unit of time with any given adjacent carbon atom. The constitution of benzene arrived at in this manner may be represented graphically by the following formulæ:



The molecule is thus supposed to oscillate between the two extreme positions. On this hypothesis any distinction between positions 1 : 2

[1] Ladenburg, *Ber.*, 1874, 7, 1684.

and 1 6 disappears, and the occurrence of more than three di-substitution products is impossible When it was first put forward, Kekulé's oscillation theory assumed the existence of a property peculiar to the benzene ring To day, in the light of our present knowledge, it may be regarded as a special case of tautomerism

In so far as their mechanism is understood, all syntheses of benzene and its derivatives appear to support the Kekulé formula As modified by the oscillation hypothesis, it would long ago have found general acceptance but for the fact that in its chemical character benzene is much less unsaturated than the olefines, and resembles rather the hydrocarbons of the saturated series Halogens, for example, only unite with difficulty with benzene, whereas they combine instantaneously with aliphatic compounds containing multiple bonds Benzene is also very stable towards oxidising agents and does not react at all with alkaline potassium permanganate, which is a specific reagent for ethylene derivatives

The advocates of the centric formula of Armstrong and Bamberger (p 356) claim to be able to explain these anomalies In this formula the fourth valencies of the carbon atoms, which cannot be utilised individually for ring formation or combination with other atoms, are supposed to be directed towards the centre of the ring, where they neutralise one another Since no such mode of linking is known in the aliphatic series, an explanation may thus be furnished of the existence of those "aromatic" properties peculiar to benzene derivatives In common with many other formulæ which have been advanced from time to time, this also has points of weakness It is difficult to see why the hypothesis of centrally directed bonds should be limited to the simple hexagon ring, but if it be applied to the polynuclear ring systems of naphthalene, anthracene, and phenanthrene, the formulæ so deduced do not harmonise with the chemical properties of these compounds

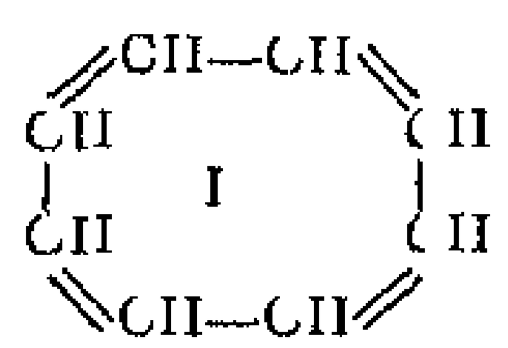
In connection with the investigation of cyclo-octatetraene, Willstatter[1] concludes that the properties of this substance support the centric formula of benzene, but not the centric formula of naphthalene In the latter he assumes the one nucleus to be saturated according to the centric formula and the other to be olefinic in character

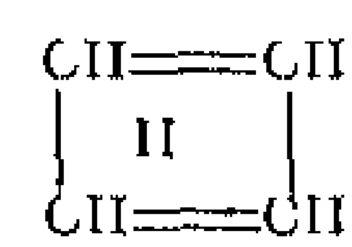
In a somewhat different manner, Thiele attempted to explain the almost completely saturated properties of the benzene ring Reference has already been made on p 23 to his work on compounds containing conjugated double bonds, as a result of which he put forward the hypothesis that the affinities in the ordinary double bond were not completely utilised, but left residual or "partial valencies" in excess Where two double bonds are in the conjugated position, the residual

[1] *Ber*, 1911, 44, 3428

valencies on the two central atoms are supposed mutually to satisfy one another. This conception has also been extended to the benzene formula of Kekulé, which represents a closed system of conjugated double bonds, and leads to the conclusion that the residual affinities of the double bonds are completely saturated, as expressed in Thiele's formula on p. 356.

Nevertheless, cyclo-octatetraene (I.) has been shown by Willstätter to be strongly unsaturated and very unstable. Cyclo-butadiene (II.) is apparently so unstable that it has not yet been isolated. Thiele's hypothesis cannot therefore be applied to all ring systems containing an alternation of single and double bonds.





According to Thiele's hypothesis, the Kekulé formula for benzene represents a saturated compound, thus bringing it into good agreement with the physical and chemical properties of the substance. This formulation will be used in the following pages.[1]

ISOMERISM IN THE BENZENE SERIES

If one of the hydrogen atoms in benzene be replaced by another element or radical, the resulting *mono-substitution product exists in one form only*. There is thus only one monochlorobenzene, C_6H_5Cl, one monoamino-benzene, $C_6H_5NH_2$, and so on.

Hence in this case the position assigned to the substituent group is immaterial, owing to the equivalence of the six hydrogen atoms.

If two hydrogen atoms of benzene are replaced by two monovalent elements or radicals,[2] the relative positions of the substituents greatly influence the properties of the compound.

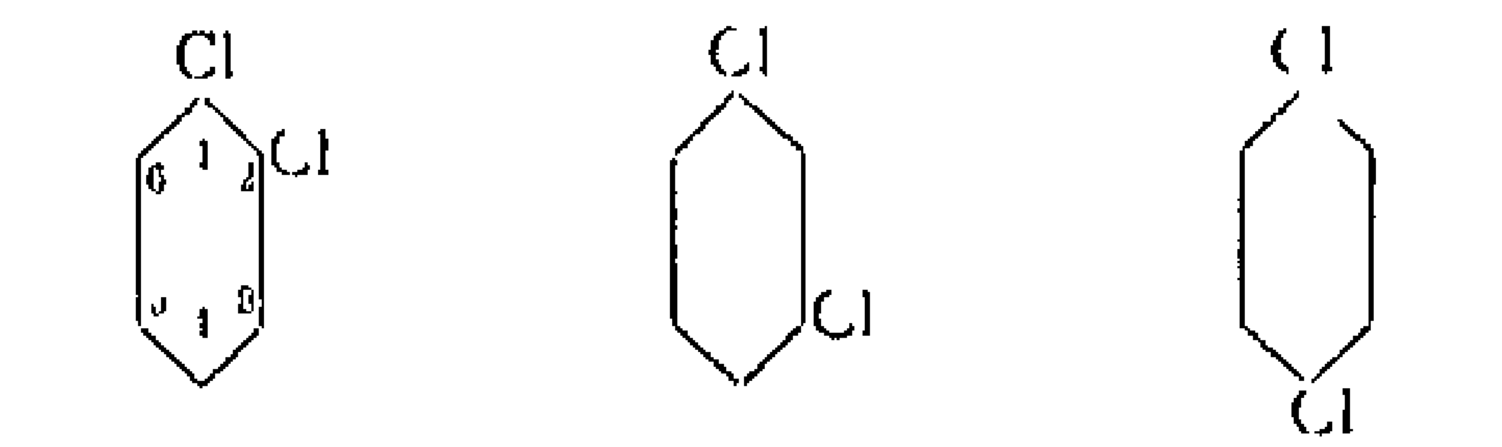
All di-substitution products exist in three isomeric forms. If we indicate the position of the first substituent with the figure 1, the three compounds formed by the introduction of a second substituent may be written as follows:

$$1 \cdot 2 = 1 \cdot 6, \quad 1 \cdot 3 = 1 \cdot 5, \quad \text{and} \quad 1 \cdot 4$$

The derivative formed by substitution in position 2 or 6 is known as an *ortho*-compound, in position 3 or 5 as a *meta*-compound, and in

[1] To simplify the formulæ and enable the relative positions of substituents to be clearly indicated, the usual custom will be followed of representing the benzene nucleus by a hexagon.
[2] A polyvalent element never replaces several hydrogen atoms simultaneously in the same benzene nucleus. Compounds such as $C_6H_4{=}O$ or $C_6H_3{\equiv}N$ are unknown.

position 4 as a *para*-compound. Usually these are contracted to *o*-, *m*-, and *p*-, or 1:2-, 1:3- and 1:4-, *e.g.*



o- or 1:2-
Dichlorobenzene

m- or 1:3-
Dichlorobenzene

p- or 1:4-
Dichlorobenzene

Even when the two substituents are different, three and only three isomerides are known.

The case is otherwise, however, when three hydrogen atoms are replaced by three monovalent elements or radicals. *If the substituents are the same, each trisubstitution product can occur in three isomeric forms.* These are distinguished from one another as vicinal (1:2:3)-, unsymmetrical (1:2:4)-, and symmetrical (1:3:5)-derivatives of benzene, and are usually written with the corresponding numbers or the abbreviation *v*-, *as*-, or *s*-, before the name of the compound, *e.g.*

v- or 1:2:3-trichlorobenzene; *as*- or 1:2:4-trichlorobenzene;
s- or 1:3:5-trichlorobenzene.

On the other hand, when the three substituents are not all the same the number of isomerides is greater than three. Should two be identical, as in the case of the compound $C_6H_3Cl(OH)_2$, six isomerides are possible; and if each of the three substituent groups is different, as in the compound $C_6H_3Cl(OH)CH_3$, theory predicts the existence of twelve isomerides.

With the entry of four similar substituents into the benzene nucleus, the number of isomerides is once again reduced to three, since the two remaining hydrogen atoms in the ring must occupy the ortho-, meta- or para-position to one another. If the four substituents are different, the number of isomers is even greater than in the case of three unlike substituents.

Finally, if five hydrogen atoms are replaced by the same element or radical, as in C_6HCl_5, there is again only one compound possible.

Aliphatic radicals such as $—CH_3$, $—C_2H_5$, or $—CH_2·CH_3$ attached to the benzene molecule are known as *side chains*, and the rest of the molecule is termed the *nucleus* or benzene nucleus. Derivatives of this type possess the character of both aromatic and aliphatic compounds, and on further substitution may yield isomerides of quite different properties, depending on whether the substituent enters the nucleus or side chain, *e.g.*

$C_6H_4Cl·CH_3$
Chlorotoluene

$C_6H_5·CH_2Cl$
Benzyl chloride

Comparison of Aromatic and Aliphatic Derivatives

The properties of benzene derivatives which serve to differentiate aromatic from aliphatic compounds depend on the peculiar character of the benzene nucleus, and may be summarised as follows —

1 A most striking feature is the ease with which hydrogen in an aromatic nucleus may be substituted by the nitro group ($-NO_2$), the sulphonic group ($-SO_3H$), or halogen As mentioned on p 100 the normal paraffins are attacked little or not at all by concentrated nitric or sulphuric acid,[1] whereas the aromatic hydrocarbons and almost all benzene derivatives are readily nitrated with concentrated nitric acid, or a mixture of the latter with concentrated sulphuric acid —

$$C_6H_6 + HO\cdot NO_2 = \underset{\text{Nitrobenzene}}{C_6H_5\cdot NO_2} + H_2O$$

With concentrated sulphuric acid alone, aromatic compounds are readily converted into sulphonic acids

$$C_6H_6 + HO\cdot SO_3H = \underset{\text{Benzene sulphonic acid}}{C_6H_5\cdot SO_3H} + H_2O$$

2 Homologues of benzene, such as $C_6H_5\cdot CH_3$ and $C_6H_5\cdot CH_2\cdot CH_2\cdot CH_3$, differ from the paraffins in the ease with which they undergo oxidation, the latter resist attack, while the former are readily oxidised to benzene carboxylic acids such as $C_6H_5\cdot COOH$

3 A peculiar property of aromatic halogen compounds as compared with the alkyl halides is the indifferent nature of the halogen atom In chlorobenzene and bromobenzene, for example, the halogen is so firmly united to the nucleus that it can only be brought into reaction with alcoholates, ammonia and amines with the greatest of difficulty

4 Aromatic amines are less basic than fatty amines, and the phenols, *e g* C_6H_5OH, are more strongly acidic than the alcohols

5 Finally, it may be mentioned that, as in the aliphatic series, the reduction of aromatic nitro-compounds leads eventually to the formation of amines, but in this case intermediate reduction products known as azo-compounds and azoxy-compounds are first obtained In addition, aromatic amines react with nitrous acid to gives diazo-derivatives These classes of compounds are only rarely found in the aliphatic series

Directive Influence of Substituents in the Benzene Nucleus[2]

The nature of a substituent already present in the benzene ring exerts a decisive influence on the position taken up by a second entrant In this connection a close relationship exists between the *ortho-* and *para-*positions which distinguishes them sharply from the *meta-*position

[1] Nitro derivatives can only be obtained from aliphatic hydrocarbons by the action of *dilute* nitric acid at high temperatures [2] Compare Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (Veit & Co, Leipzig, 1910)

The hydroxyl group (OH), amino group (NH_2) and alkyl groups, for example, direct a newly entering element or radical preferably to the *o*- and *p*-positions, whereas a group such as NO_2 or SO_3H directs mainly to the *m*-position In general, *o*, *p*-directive groups facilitate further substitution, whilst those of *m*-directive type increase its difficulty

Many attempts have been made to classify elements and radicals according to their directive influence, some of the more important of which may be mentioned briefly

Among the earliest suggestions are those advanced independently by *Hubner*, *Nolting* and *Korner* about 1875, according to which basic or weakly acidic groups (NH_2, CH_3, OH, Cl) direct to the *o*- and *p*-positions, whereas strongly acidic groups (COOH, NO_2, SO_3H) lead to *m*-substitution

The *Crum Brown and Gibson rule*[1] states that if the radical already present (CHO, COOH, NO_2, SO_3H) forms a compound with hydrogen which can readily be converted by direct oxidation into the corresponding hydroxyl compound, the second substituent will enter the meta-position Otherwise it will assume the ortho- and para-positions

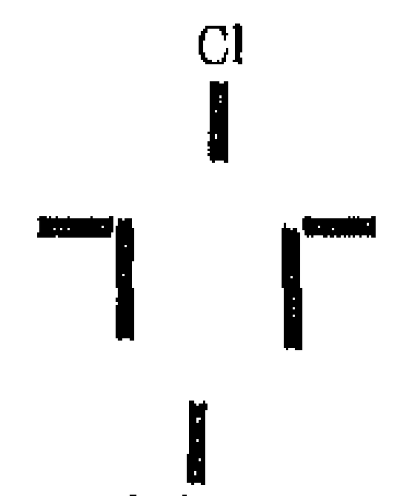
Vorlander's rule divides substituents into unsaturated groups (NO_2, CN, COOH and SO_3H) causing *m*-substitution, and saturated substituents (Cl, Br, OH, CH_3) leading to *o*- and *p*-substitution

Unfortunately, although these rules apply to the majority of the simpler cases, they are subject to exceptions and on occasion are mutually contradictory Cinnamic acid, for example, with the acidic unsaturated substituent —CH=CH—COOH, nitrates in the ortho- and para-positions Moreover, the normal directive influence of COOH or NH_2 may be largely reversed by ionisation Sodium benzoate in an aqueous solution is chlorinated in the *o*- and *p*-positions, and aniline in the presence of a large excess of sulphuric acid is nitrated mainly in the *m*-position

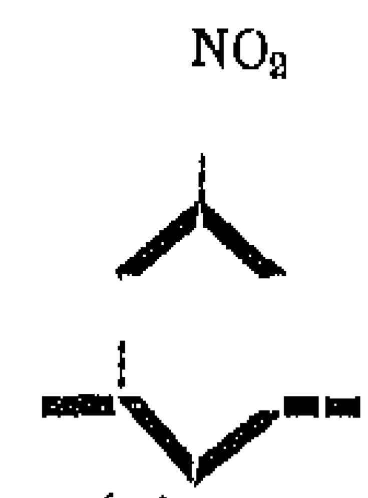
Mechanism of Substitution —Flurscheim[2] has advanced a theory of benzene substitution based on Werner's hypothesis of maximum disposable affinity When at any bond in a chain hydrogen is replaced by a substituent which differs from it in the amount of its "affinity demand," there results an alternating increase and decrease in the affinity content of successive bonds in the chain and a corresponding alternating increase and decrease of residual affinity at successive atoms (see p 83) Atoms which are capable of combining with varying equivalents of other atoms are in their lower state of combination endowed with considerable residual affinity (*e g* N in NH_2 and O in OH) When they replace hydrogen linked to carbon their affinity demand therefore exceeds that of hydrogen The contrary state of

[1] *J C S*, 1892, 61, 367 [2] *J pr Ch*, 1902, 66, 321, *Ber* 1906, 39, 2015, *J S C I* (*Chem and Ind*), 1925, 44, 246

affairs holds when atoms enter a bond in their highest state of combination (*e g* N in NO_2, S in $—SO_3H$), in which case their affinity demand is less than that of hydrogen According to the nature of the substituent present, the resulting alternation in a monosubstituted benzene is thus supposed to lead to an increase of free affinity at the *o*- and *p*-carbon atoms (*o*, *p*-substitution) or at the *m*-carbon atom (*m*-substitution)



o, *p* Substitution



m Substitution

Addition Hypothesis of Holleman[1] In the Kekulé formula for benzene a substituent X is always attached to a doubly bound carbon atom, and in such a structure it is known to have a low reactivity (see p 125)

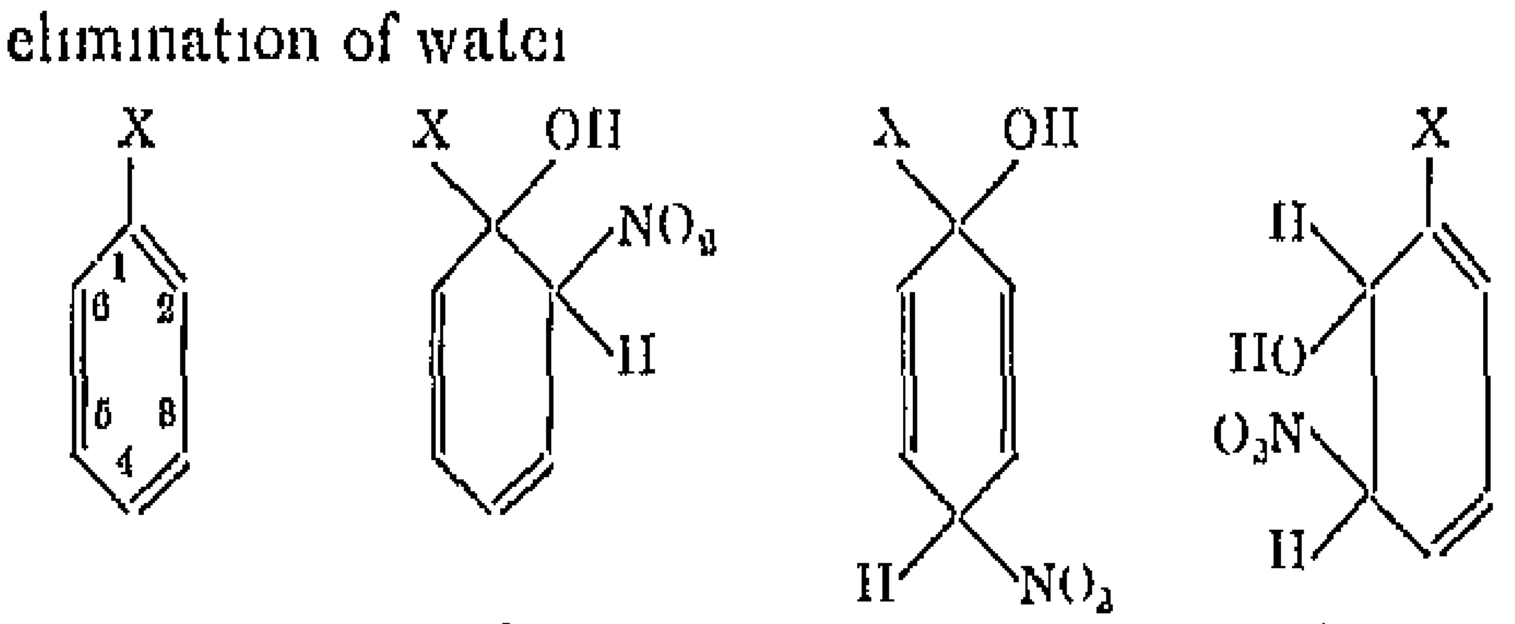
CH_2 CCl CH_3 — Non reactive halogen

CH_2 CH CH_2Cl — Reactive halogen

Since the presence of the double bond thus influences the activity of X, Holleman suggests that the converse also holds true, and that the nature of X affects the character of the double bond

According to Holleman the essential factor controlling the course of benzene substitution is the influence of X in facilitating or inhibiting addition to the adjacent double bond, and as this bond is part of a conjugated system the influence will also be propagated to the 1 4-position The 5 6-bond is assumed to be comparatively unaffected

Nitration is supposed to occur as a result of the two processes
1 Addition of reagent, which may proceed in three ways, followed by
2 rapid elimination of water



Ortho Para Meta

The type of reaction product will depend on the relative velocities of formation of the three addition compounds shown If X makes the adjoining double bonds more reactive than a normal (5 6) bond, addition takes place leading to *o*- and *p* substitution If on the other

[1] *Rec trav Chim*, 1895, 14, 123 *Chem Reviews*, 1924, I, 187

hand activity is diminished, addition occurs at the 5 6-position and *m*-substitution ensues A similar explanation is applied to the case of halogens, hydrogen halide being eliminated

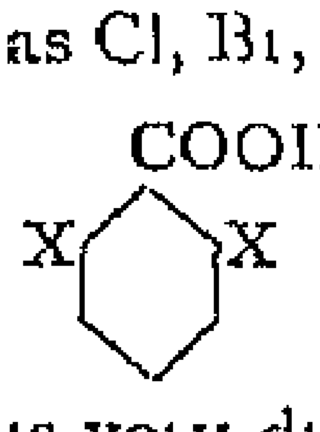
Electronic theories of benzene substitution have also been put forward by Fry and more recently by Robinson[1] and Ingold[2] For further information reference should be made to the original literature

Reactivity of Benzene Derivatives

Although halogen attached directly to the benzene nucleus does not readily enter into reaction, it may do so under the influence of other substituents present in the ring For example, the occurrence of a nitro-group in the ortho- or para-position to a halogen atom increases the reactivity of the latter, rendering it more readily exchanged for other groups or atoms The same substituent in the meta-position, on the other hand, does not induce this change Similarly bromine in *o* bromobenzoic acid is very reactive in the presence of copper acetate or copper powder When an aqueous solution of the acid is boiled for a short time with a mixture of sodium acetate and copper acetate it is converted into salicylic acid With sodio-malonic ester in the presence of copper powder, the acid yields *o* carboxyphenyl malonic ester[3] Under these conditions the chloro acid is non-reactive

Phenoxy and alkoxy groups have the property of increasing the reactivity of an α bromine atom contained in a hydrocarbon radical in the ortho- or para-position to them, *e g* o-CH_3O C_6H_4 CH_2Br[4]

Ortho-substituents occasionally exert a surprising influence in hindering or even completely preventing the progress of such reactions as would otherwise proceed with ease Numerous examples of *steric hindrance* of this type will be met with in the following pages, the best known instances being those discovered by Victor Meyer[5] in connection with the *esterification of aromatic acids* It is found that whenever the two hydrogen atoms in the ortho-positions to the carboxyl group of benzoic acid are replaced by atoms or radicals such as Cl, Br, NO_2, CH_3, or COOH, the resulting acid (see annexed formula) cannot be esterified with alcohol and hydrochloric acid, or only with extreme difficulty Similarly, if an acid of this type is once converted into its ester by other means (*e g*, by use of the silver salt and ethyl iodide), the ester is very difficult to hydrolyse



[1] R Robinson, *J C S I*, *Chem and Ind*, 1925, 44, 456 Also *J C S*, 1922, 121, 427, 1926, 308, 1655, 1927, 2411 *Chem and Ind*, 1927, pp 118, 260 [2] For summaries containing references to the original papers see *Ann Rep Chem Soc*, 1926, 129, 1927, 148, 1928, 137 [3] W R H Hurtley, *J C S*, 1929, 1870 [4] A Werner, *Ber*, 1906, 39, 27, for a suggested explanation, see A Lapworth and J B Shoesmith, *J C S*, 1922, 121, 1391 [5] *Ber*, 1894, 27, 510, 1580, 3146, 1895, 28, 182, 1254, 2773, 3197, 1896, 29, 839, 1397, 1830, 2564, 1897, 30, 1277

Formation of Cyclic from Open-chain Compounds

Aliphatic compounds may be transformed into those of the aromatic series in a number of ways, one of which is of historical interest and has already been referred to on p 255 A few of the more important methods are given below

1 When submitted to a high temperature, many methane derivatives yield benzene compounds among other products

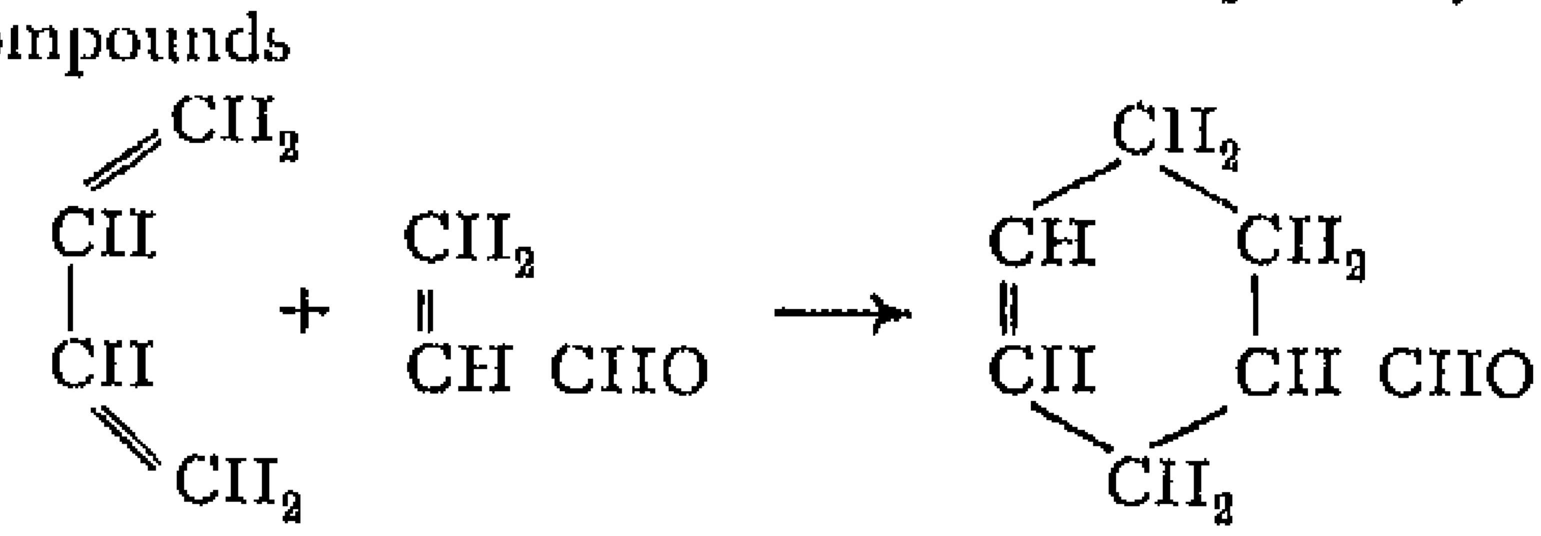
2 In the same manner acetylene polymerises to benzene, $3C_2H_2 = C_6H_6$, and other aromatic hydrocarbons,[1] monobromo acetylene gives 1 3 5-tribromo benzene, $3C_2HBr = C_6H_3Br_3$, treatment with concentrated sulphuric acid converts allylene into mesitylene or 1 3 5-trimethyl-benzene, $3CH\ C\ CH_3 = C_6H_3(CH_3)_3$

3 Acetone also yields mesitylene when treated with sulphuric acid, $3CH_3\ CO\ CH_3 = C_6H_3(CH_3)_3 + 3H_2O$ In a similar manner methyl-ethyl-ketone, $CH_3\ CO\ C_2H_5$, gives 1 3 5-triethyl-benzene, $C_6H_3(C_2H_5)_3$, and formylacetone, $CH_3\ CO\ CH_2\ CHO$, passes rapidly into 1 3 5-triacetyl-benzene, $C_6H_3(CO\ CH_3)_3$

4 Potassium combines directly with carbon monoxide to form the potassium salt of hexahydroxy-benzene

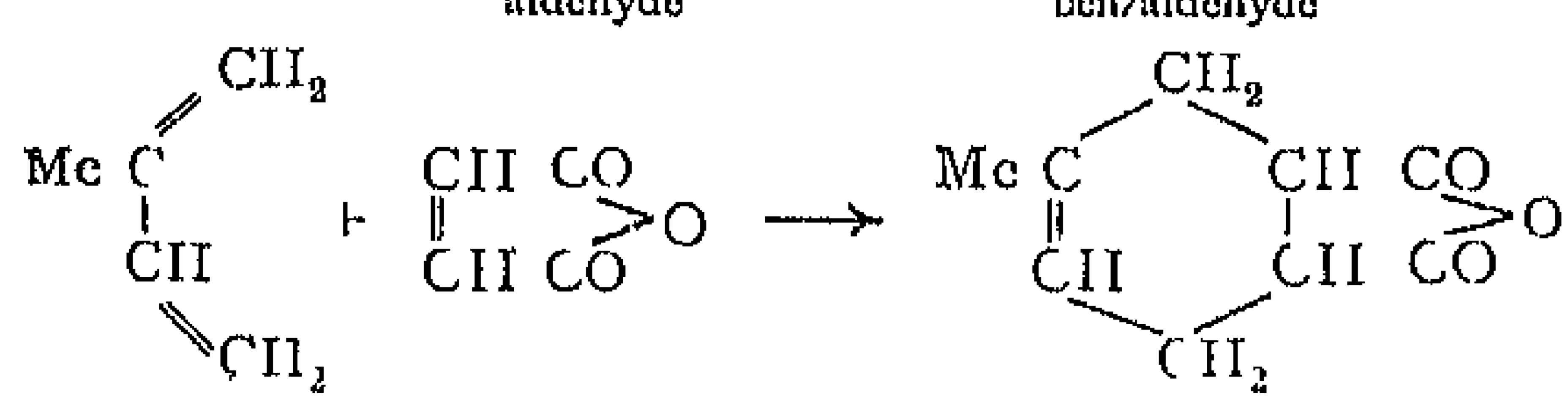
5 A valuable reaction of unsaturated compounds has been investigated by Diels and Alder Butadiene and many of its derivatives have been found to react quantitatively with substances containing the group CH CH CO , such as maleic anhydride, acrylic aldehyde, acrylic ester[2] In many cases the interaction proceeds at room temperature Combination occurs by the reactive group CH CH CO adding terminally to the butadiene, as in the following typical examples, resulting in the production of partially hydrogenated aromatic compounds

I.



Butadiene Acrylic aldehyde Tetrahydro benzaldehyde

II

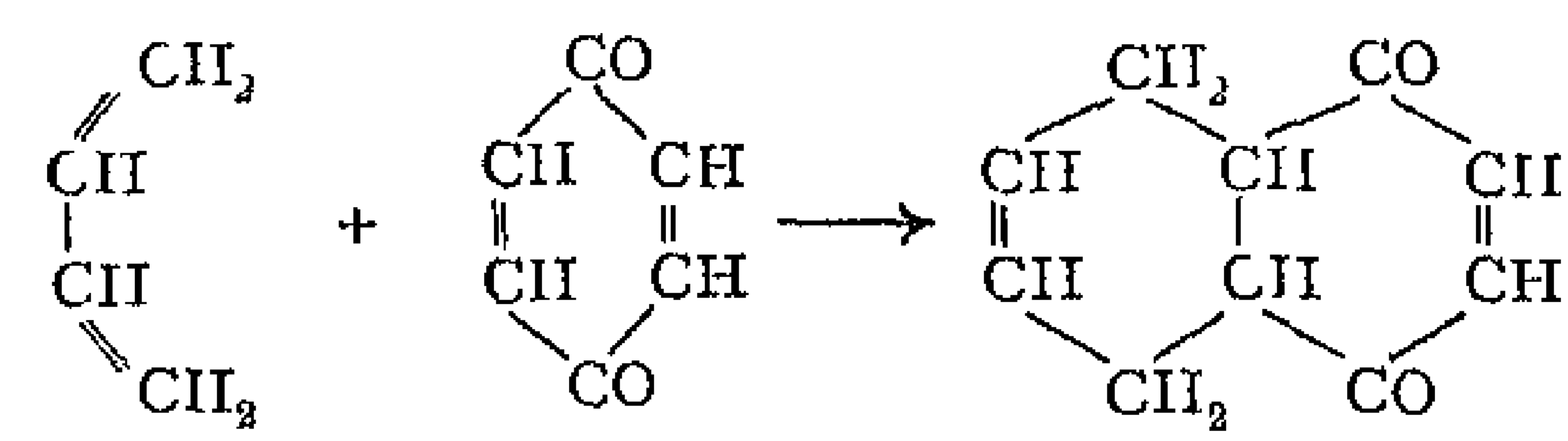


Isoprene Maleic anhydride Methyl tetrahydro-phthalic anhydride

[1] R Meyer and A Tanzen, *Ber*, 1913, 46, 3183 [2] O. Diels, K Alder and co workers, *Ann*, 1928, 460, 98, 1929, 470, 62 *Ber*, 1929, 62 B, 554, 2081 See also F H Farmer, *Ann Rep Chem Soc*, 1930, 88, where a number of other references will be found

This reaction is capable of very wide extension, for example, the place of the above aliphatic keto-compounds may be taken by *p*-benzoquinone and α-naphthaquinone,

III



and that of butadiene by a variety of cyclic unsaturated hydrocarbons

On the other hand, certain benzene derivatives, particularly phenols, aminophenols, quinones, hydroxy-quinones and phenol-carboxylic acids, may be converted into open chain compounds Thus benzene triozonide decomposes with water to give glyoxal, mesotartaric acid (see p 281) has been obtained by the oxidation of phenol, C_6H_5OH, with dilute permanganate solution, and chloroquinone and finally maleic acid are formed when benzene is treated with potassium chlorate and sulphuric acid

III

Benzene and its Homologues

Benzene is formed during the dry distillation of coal, and, as described in detail below, is prepared industrially from coal tar It was first isolated by Faraday in 1825 from the illuminating gas obtained from oil, it was prepared from benzoic acid by Mitscherlich in 1834, and its presence in coal tar discovered in 1845 by A W Hofmann

Benzene is a colourless, strongly refracting liquid of peculiar aromatic taste and smell, boiling at 80 4° under 760 mm and melting at +5 4° Sp gr 0 899 at 0° It burns with a luminous sooty flame, is insoluble in water, but is miscible in all proportions with alcohol and ether, and forms an excellent solvent for resins, fats and sulphur With an ammoniacal solution of nickelous cyanide it yields a white, violet-tinted crystalline compound of the formula NiC_2N_2, NH_3, C_6H_6, which may be used for the detection of benzene,[1] and with antimony pentachloride, according to the amount of solvent present, a yellow to yellow-red colour is developed[2] When treated with chlorine, benzene forms both addition and substitution products, such as $C_6H_6Cl_2$, $C_6H_6Cl_4$, $C_6H_6Cl_6$ and C_6H_5Cl, $C_6H_4Cl_2$

Concentrated sulphuric acid converts it into benzene sulphonic

[1] K A Hofmann and Arnoldi, *Ber*, 1906, 39, 339 [2] S. Hilpert and Wolf, *Ber*, 1913, 46, 2215

acid, nitric acid into nitrobenzene, and hydriodic acid into hexahydrobenzene With ozone, benzene yields a triozonide, $C_6H_6(O_3)_3$, which is decomposed by water[1] to form glyoxal

$$C_6H_6(O_3)_3 \longrightarrow 3O\ CH\ CH\ O$$

These and other chemical changes of benzene are discussed in detail in later chapters

DRY DISTILLATION OF COAL AND MANUFACTURE OF COAL GAS

The main source of benzene and its methyl homologues is the tar obtained as a by-product when coal is submitted to dry distillation at temperatures above 1000° C, either for the manufacture of coal gas or of coke for metallurgical purposes In the former process, gas coals are employed, rich in hydrogen and yielding a high proportion of gas, whereas in coke ovens a coal poorer in hydrogen is utilised, which will give a good yield of a dense coke Gas coke of open texture is, in addition, produced in relatively small amount in the manufacture of coal gas, and gas is also obtained from the coke ovens Coal tar and an aqueous liquor containing ammonia (gas liquor) are obtained as by-products in both processes

The distillation of gas coal is carried out in retorts of fireproof clay Volatile products of decomposition are led through pipes to a trough, in which the bulk of the tar condenses Coal gas passes on, and is freed from further quantities of tar and ammoniacal gas liquor by passage through specially constructed chambers which are well cooled with water The remainder of the ammonia is removed by washing the gas in water The gas is next freed from hydrogen cyanide, usually by washing with a solution of an iron salt, the resulting cyanogen compounds of iron being subsequently worked up for potassium ferrocyanide and other products Finally, sulphur is removed, generally by leading the gas through cast-iron chambers containing hydrated ferric oxide spread out in thin layers

The purified coal gas is collected over water in gas-holders or gasometers, and delivered under pressure into distributing pipes It contains hydrogen (about 50 per cent by volume), methane (35 per cent) and carbon monoxide (8 per cent) as non-luminous constituents, and ethylene, acetylene, benzene and naphthalene (totalling about 4 per cent) as luminous constituents, together with carbon dioxide (1 per cent), nitrogen (4 per cent), hydrogen sulphide and ammonia as impurities

From 100 kilos of coal are obtained on the average 27 to 30 cubic metres of gas, 5 kilos tar, 64 kilos coke and 100 kilos of ammoniacal gas liquor

[1] Harries, *Ann*, 1905, 343, 335

Up to the present time, the distillation of coal by the above process has usually been so conducted that the primary products of distillation are—by contact with the red-hot walls of the retort—largely converted into compounds of an aromatic nature, which collect in the tar. According to recent investigations, the **low temperature distillation of coal** may be effected at 600° under reduced pressure, to give a large primary *distillate of aliphatic character*.[1] In this manner the typical products of the petroleum industry may be prepared from coal (see pp. 101 and 106).

The yield of tar from the low temperature process varies, according to the starting material, from 8 to 12 parts as against the 4 to 5 parts obtained from the ordinary process in the manufacture of coal gas. The low temperature tar may be prepared either as the chief product of distillation in apparatus designed to this end, or as a by-product from the gas generator.

Coal Tar

Properties, Composition and Uses.—Coal tar as obtained from the manufacture of coal gas or the coke ovens is a black, viscous liquid of peculiar acrid smell. It is an extremely complex mixture of substances, which may be roughly divided into those of acidic, basic and neutral character. Among neutral products, the most important are the hydrocarbons of the aromatic series—benzene and its homologues, naphthalene and anthracene—to which the industrial value of coal tar is mainly due. The content of naphthalene amounts to 5 to 10 per cent. of the tar, and of benzene and toluene to about 1 to 1.5 per cent. Basic constituents include compounds of the pyridine and quinoline group, while those of acidic nature are chiefly phenols, among which phenol itself predominates.

Coal tar is probably put to a greater variety of uses than any other substance. In the crude state, without any previous rectification, it is used for protecting the surface of masonry and wood, for impregnating wood, in the preparation of composition roofing, in the manufacture of lampblack and briquettes, and as fuel. Its chief value, however, lies in the products which can be obtained from it.

Distillation of Coal Tar.—Distillation is carried out in roomy stills which are bricked in, and the distillate is condensed in an iron coil condenser. Four fractions are usually collected as follows:—

1. *Light oil*, which is lighter than water and distils between 80° and 170°.

2. *Middle or carbolic oil*, sp. gr. approximately 1, which distils between 170° and 240°.

3. *Heavy or creosote oil*, which is heavier than water and distils between 240° and 270°.

[1] See *Low Temperature Carbonisation of Bituminous Coal*, by McCulloch and Simpkin (Witherby, 1923).

4 *Green or anthracene oil*, which is green in colour and distils between 270° and 400°.

The *pitch* which is left as a residue in the retort is utilised in the preparation of varnish and lacquer, briquettes and other products.

For the production of benzene hydrocarbons the only fraction of importance is the light oil. This is washed with aqueous sodium hydroxide to remove acids, and with concentrated sulphuric acid to remove bases, and is then fractionated in a rectifying column. Benzene, toluene, $C_6H_5 \cdot CH_3$, and xylenes or dimethyl-benzenes, $C_6H_4(CH_3)_2$, are thus obtained in a relatively pure form, and are placed directly on the market. Methyl derivatives such as the three isomeric xylenes, and the trimethyl-benzenes or cumenes, are rarely isolated in the pure state from light oil, but are usually employed in the crude condition as solvents for resins, fats, and so on.

Like the other alkyl derivatives of benzene, they are also prepared synthetically.

Preparation of Benzene Homologues

Alkyl derivatives of benzene may be prepared by the condensation of alkyl-acetylenes (see p. 365) and by the following methods:—

1. By the dry distillation of aromatic carboxylic acids with alkali. In the same manner benzene may be obtained from benzoic acid.

$$C_6H_5 \cdot CO_2Na + NaOH = C_6H_6 + Na_2CO_3$$

2. By the action of sodium on a mixture of a brominated benzene hydrocarbon and an alkyl bromide or iodide, *e.g.*

$$C_6H_5Br + 2Na + C_2H_5Br = \underset{\text{Ethyl-benzene}}{C_6H_5 \cdot C_2H_5} + 2NaBr$$

This reaction, discovered by Fittig, is an extension of the Wurtz method of synthesising paraffins by the use of sodium and alkyl halides (p. 102).

3. From aromatic organo-magnesium derivatives by heating with alkyl halides, or more conveniently by the action of alkyl sulphates.[1]

$$\underset{\substack{\text{Phenyl magnesium}\\ \text{bromide}}}{C_6H_5 \cdot MgBr} + \underset{\substack{\text{Dimethyl}\\ \text{sulphate}}}{(CH_3)_2SO_4} = \underset{\substack{\text{Methyl benzene}\\ \text{or toluene}}}{C_6H_5 \cdot CH_3} + Br \cdot Mg \cdot SO_4CH_3$$

In this connection it may be noted that alkylene benzene derivatives (1^1-alkylated styroles), which are readily synthesised from alkyl magnesium halides (see p. 373), are easily reduced to the corresponding benzene hydrocarbons, thus providing a valuable means of preparing a series of otherwise difficultly accessible compounds. In this manner propenyl-benzene, $C_6H_5 \cdot CH : CH \cdot CH_3$, yields

[1] Werner and Zilkens, *Ber.*, 1903, 36, 2116, 3618. Houben, *Ber.*, 1903, 36, 3083; 1904, 37, 488.

n-propyl-benzene, $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_3$, and methovinyl-benzene, $C_6H_5 \cdot C(CH_3) : CH_2$, yields isopropyl-benzene, $C_6H_5 \cdot CH(CH_3) \cdot CH_3$.

4. The *Friedel-Crafts reaction*[1] is another important method of preparing alkyl-benzenes. This consists in bringing aromatic hydrocarbons into reaction with alkyl halides, in the presence of anhydrous aluminium chloride:[2]

$$C_6H_6 + Br \cdot C_2H_5 = \underset{\text{Ethyl benzene}}{C_6H_5 \cdot C_2H_5} + HBr$$

$$\underset{\text{Toluene}}{C_6H_5 \cdot CH_3} + Cl \cdot CH_3 = \underset{\text{Xylene}}{C_6H_4(CH_3)_2} + HCl$$

By this method all the hydrogen atoms of benzene may be replaced in turn by alkyl groups, although it is often difficult to stop the action at the desired point and to separate the mixture of isomerides formed. The reaction is still further complicated by the fact that the aluminium chloride tends to detach the alkyl groups already introduced, *e.g.*

$$C_6H_5 \cdot CH_3 + HCl = C_6H_6 + CH_3Cl$$

In spite of these drawbacks, however, the Friedel-Crafts reaction has proved of great value in the synthesis of benzene homologues and other aromatic compounds.

5. Benzene and its homologues may also be regenerated from the corresponding sulphonic acids by heating them with superheated steam in the presence of sulphuric acid, concentrated hydrochloric acid or phosphoric acid:

$$C_6H_3(CH_3)_2SO_3H + H_2O = C_6H_4(CH_3)_2 + H_2SO_4$$

This reaction often provides a convenient method of separating a mixture of hydrocarbons. If, for example, one hydrocarbon can be sulphonated under certain conditions and another not, the latter can easily be extracted from the reaction mixture and the sulphonic derivative of the former then converted back into the hydrocarbon by the above means.

Properties and Reactions of the Alkyl-benzenes

The alkyl-benzenes are generally colourless liquids with a smell like that of benzene. They are insoluble in water but soluble in alcohol and ether. The introduction of a methyl group into the nucleus raises the boiling-points of the methyl-benzenes about 24° to 30°; if introduced into the side chain the rise is about 24°. Towards chlorine, bromine, sulphuric acid and concentrated nitric acid they behave in the same manner as benzene, the hydrogen of the nucleus undergoing substitution.

A characteristic property of these hydrocarbons which is of great value for their identification is their behaviour on oxidation. Treatment with dilute nitric acid, chromic acid mixture, potassium perman-

[1] *Ber.*, 1881, 14, 2627; Boeseken and Bastet, *C.*, 1914, I, 647. [2] Ferric chloride acts in a similar manner; Nencki, *Ber.*, 1897, 30, 1766; 1899, 32, 2414.

ganate, or ferricyanide converts each side chain into a carboxyl group (COOH), by the same intermediate steps as in the case of aliphatic compounds From the number and relative position of the resulting carboxyl groups it is possible to deduce the number and position of the alkyl radicals originally present

Thus a hydrocarbon C_9H_{12} might have either of the constitutions

$C_6H_5 \cdot C_3H_7$	$C_6H_4\begin{cases}CH_3\\C_2H_5\end{cases}$	$C_6H_3(CH_3)_3$
Propyl or isopropyl benzene	One of the three methyl ethyl benzenes	One of the three trimethyl benzenes

On oxidation, the first compound yields benzoic acid, $C_6H_5 \cdot COOH$, each of the three methyl ethyl benzenes gives a different dicarboxylic acid, $C_6H_4(COOH)_2$, and each of the three trimethyl benzenes a different tricarboxylic acid, $C_6H_3(COOH)_3$

Toluene, *methyl-benzene*, $C_6H_5 \cdot CH_3$, occurs among the products of dry distillation of a number of substances, particularly of Tolu balsam (*Toluifera balsamum*), from which Berzelius first derived its name

It may be obtained synthetically according to the foregoing methods, (1) by the action of sodium on a mixture of methyl iodide and bromobenzene in dry ethereal solution, (2) by leading methyl chloride into benzene in the presence of aluminium chloride, (3) from phenyl magnesium bromide and dimethyl sulphate in dry ethereal solution, and (4) by the dry distillation of a mixture of sodium benzoate and sodium acetate Toluene may also be prepared from toluene sulphonic acids and by the distillation of *p*-toluic acid

On the technical scale the only source of toluene is coal tar

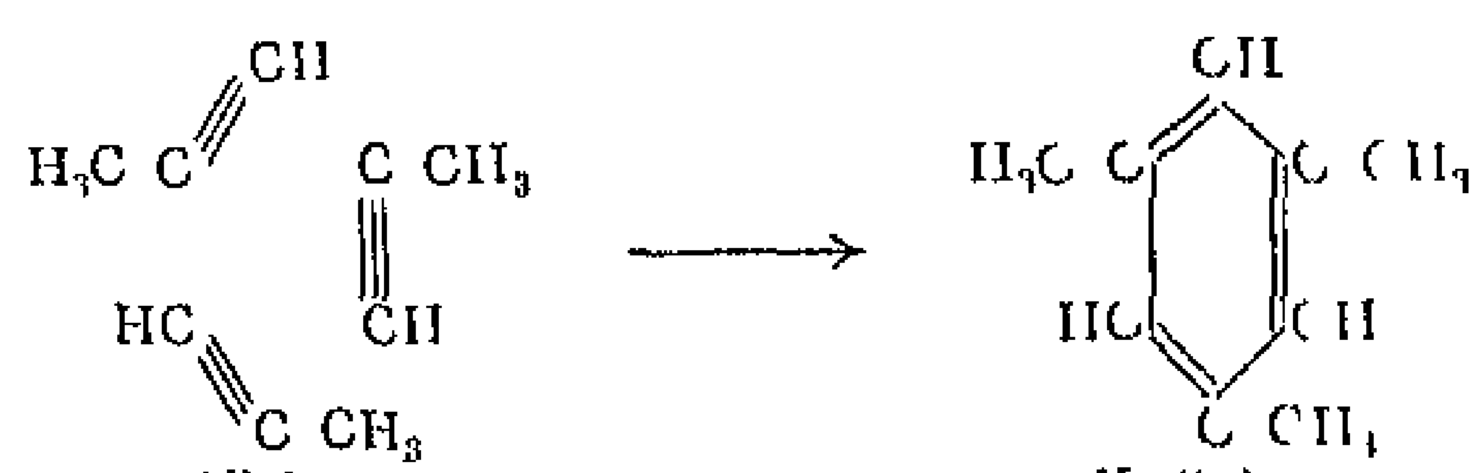
Toluene is a colourless, mobile, and strongly refractive liquid, which freezes at $-94°$ and boils at $110°$, sp gr $\cdot 8841$ at $0°$ It is practically insoluble in water but it readily mixes with alcohol, ether and chloroform It burns with a very smoky flame, dissolves sulphur, phosphorus, iodine, fats and resins, and is largely used as a solvent for phosgene When oxidised with potassium bichromate and sulphuric acid, or with dilute nitric acid, toluene is converted into benzoic acid On reduction it forms hexahydro-toluene The behaviour of toluene towards chromyl chloride has been studied by Etard In carbon disulphide solution a compound of the composition $C_7H_8, 2CrO_2Cl_2$ is obtained, which decomposes with water to form benzaldehyde.

The action of chlorine on toluene varies with the temperature At higher temperatures substitution occurs in the side chain, and at low temperatures in the nucleus Chlorine passed into boiling toluene leads first to the formation of benzyl chloride, $C_6H_5 \cdot CH_2Cl$, which then yields benzal chloride, $C_6H_5 \cdot CHCl_2$, and finally benzo-trichloride, $C_6H_5 \cdot CCl_3$ In the cold, on the other hand, *o*- and *p*-chlorotoluenes, $C_6H_4Cl \cdot CH_3$, are formed On nitration, toluene yields a mixture of

the three possible mono derivatives, chiefly the *o*- and *p* compounds, with a considerably smaller proportion of *m*-nitrotoluene

Xylenes, *dimethyl benzenes*, $C_6H_4(CH_3)_2$, are found in coal tar, the most valuable isomeride, iso or *m* xylene, being present in the greatest proportion They are colourless liquids which distil at approximately the same temperature,[1] *o* xylene boils at 142°, *m* xylene at 139°, and *p* xylene at 138°

Trimethyl benzenes, $C_6H_3(CH_3)_3$ Of these, hemimellitol (1 2 3) boils at 175°, pseudocumene (1 2 4) at 170°, and mesitylene (1 3 5) at 164° All three occur in coal tar Mesitylene is formed by the action of concentrated sulphuric acid on acetone or allylene, $3CH_3\ CO\ CH_3 = C_6H_3(CH_3)_3 + 3H_2O$



Allylene Mesitylene

The proof of its symmetrical structure was of great importance in determining the orientation of benzene substitution products

Cymene, p *methyl-isopropyl-benzene*, $C_6H_4\begin{cases}CH_3\\CH(CH_3)_2\end{cases}$, is found in various ethereal oils (oil of thyme and oil of eucalyptus), and may be obtained from camphor, oil of turpentine and certain other terpenes It is a pleasant-smelling liquid, which boils at 175° and can be synthesised from *p*-bromo-isopropyl-benzene, methyl iodide and sodium

Pentamethyl-benzene melts at 53° and boils at 230°

Hexamethyl-benzene may be prepared by leading an equimolecular mixture of methyl alcohol and acetone in the vaporous form over heated aluminium oxide[2] It melts at 164° and boils at 264°

Benzene Hydrocarbons with Unsaturated Side Chains

These show, on the one hand, the properties characteristic of aromatic compounds, and on the other those of the unsaturated hydrocarbons of the aliphatic series (see p 108) They readily unite with hydrogen and halogens

Alkylene benzene derivatives can be prepared by means of the Grignard reaction, either directly or by the elimination of water from the carbinols obtained in such variety by this reaction from aldehydes, ketones, esters and alkyl halides Their direct formation occurs particularly in those cases where an excess of the Grignard reagent

[1] These isomerides cannot be separated by distillation For a method involving the use of sulphuric acid, see *Ber*, 1877, **10**, 1010, 1881, **14**, 2625, 1884, **17**, 144 [2] Reckleben and Scheiber, *Ber*, 1913, **46**, 2363

is employed, and the reaction mixture, after evaporation of the ether, is heated for some time,[1] e g

$$C_6H_5\,C\!\begin{smallmatrix}\diagup CH_3\\ \diagdown O\end{smallmatrix} \xrightarrow[+\,CH_3MgI]{} C_6H_5\,C\!\begin{smallmatrix}\diagup CH_3\\ -CH_3\\ \diagdown OMgI\end{smallmatrix} \longrightarrow C_6H_5\,C\!\begin{smallmatrix}\diagup CH_3\\ \diagdown\!\diagdown CH_2\end{smallmatrix}$$

Styrene, *phenyl ethylene*, *vinyl benzene*, $C_6H_5\cdot CH:CH_2$, is the simplest representative of the olefine derivatives It is present in storax and is a colourless, strongly refracting liquid, b p 146°, with a smell resembling that of benzene It is obtained from cinnamic acid by heating with lime It may also be prepared from ethyl benzene,[2] $C_6H_5\cdot C_2H_5 \longrightarrow C_6H_5\cdot CHBr\cdot CH_2Br \longrightarrow C_6H_5\cdot CH:CH_2$ At 200° it polymerises to a solid compound called metastyrene[3] On reduction it yields ethyl benzene, $C_6H_5\cdot CH_2\cdot CH_3$, and with bromine forms two isomeric dibromides, $C_6H_5\cdot CHBr\cdot CH_2Br$

Phenyl acetylene, $C_6H_5\cdot C{\equiv}CH$, is a derivative of acetylene It can be obtained by a variety of methods, such as from phenylpropiolic acid, $C_6H_5\cdot C{\equiv}C\cdot COOH$, by splitting off carbon dioxide, or from dibenzal acetone tetrabromide by treatment with alcoholic potash[4] It is a pleasant smelling liquid, b p 142°, which like acetylene gives explosive metallic derivatives with ammoniacal silver nitrate or cuprous chloride solutions When boiled with zinc dust and acetic acid, it takes up hydrogen and is converted into styrene, $C_6H_5\cdot CH:CH_2$ Under the influence of dilute sulphuric acid, phenyl acetylene combines with water to form acetophenone, $C_6H_5\cdot CO\cdot CH_3$

IV

Halogen Derivatives of the Aromatic Hydrocarbons, and their Magnesium Compounds

Halogen substitution products of the aromatic hydrocarbons can be prepared by the following methods —

1 By the action of halogen on the hydrocarbon In the case of iodine the hydriodic acid set free during the reaction must be removed as fast as it is formed The hydrocarbon is therefore heated with iodine and an oxidising agent[5] such as mercuric oxide, iodic acid, or a persulphate It has already been mentioned under toluene that chlorine and bromine may enter either the side chain or the nucleus, according to experimental conditions

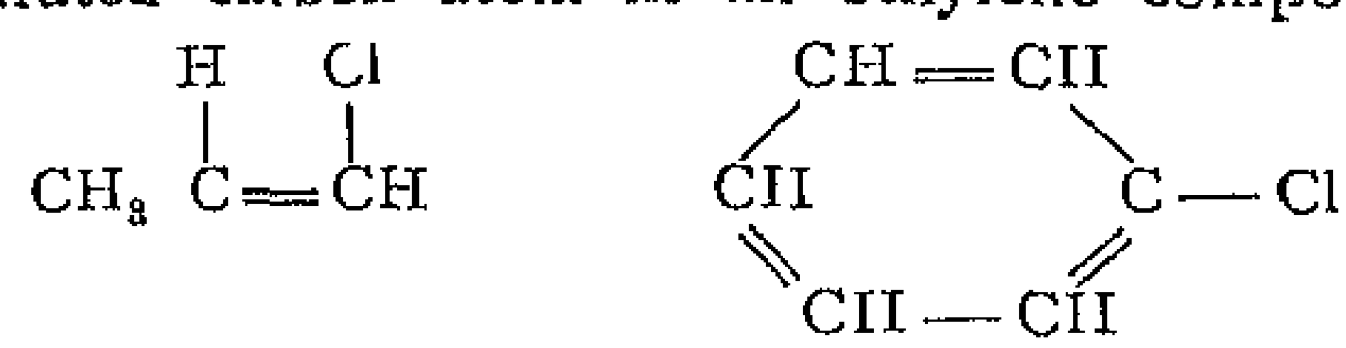
2 From the diazo-compounds (see p 395) by interaction with cuprous chloride or bromide, or with potassium iodide

$$C_6H_5N_2Cl = C_6H_5Cl + N_2$$

3 A simple method of brominating aromatic compounds[6] consists in shaking them at ordinary temperatures with an aqueous solution of hypobromous acid

[1] Klages, *Ber*, 1902, 35, 2633, 3506, 1904, 37, 649, 1447 C Hell, *Ber*, 1904, 37, 225, 230, 453, 1429, 4188 [2] J v Braun and Moldänke, *Ber*, 1921, 54, 618 [3] Stobbe, *Ann*, 1909, 371, 259 [4] G Mühlhausen, *Ber*, 1906, 39, 4146 [5] K Elbs and Jaroslawzew, *J pr Ch* [2], 1913, 88, 92 [6] O Stark, *Ber*, 1910, 43, 670

In their chemical behaviour the aromatic halogen compounds are distinguished above all by the stability of the halogen atom directly attached to the nucleus. This halogen cannot be exchanged directly for other groups such as OH and NH_2, as in the saturated aliphatic derivatives, but resembles the relatively non-reactive halogen linked to an unsaturated carbon atom in an ethylene compound (p. 125).



Nevertheless it should be noted that the entrance of further substituents into the molecule may increase the reactivity of the halogen in this sense; compounds which contain one or two nitro groups in the ortho position to the halogen exchange the latter as readily as the alkyl halides[1]; similarly the bromine in *o*-bromobenzoic acid is reactive (p. 364). In certain cases halogen attached directly to the nucleus may be brought into reaction by the use of catalysts or ultraviolet radiation[2]. In aromatic compounds such as benzyl chloride, $C_6H_5\cdot CH_2Cl$, the halogen atom in the aliphatic side chain is comparatively reactive.

From the practical standpoint it is of considerable importance that aromatic halogen compounds resemble those of the aliphatic series in undergoing the *Grignard reaction*. When treated in dry ethereal solution with metallic magnesium they form compounds of the general formula R·Mg·Hal (see p. 127).

$$\underset{\text{Phenyl bromide}}{C_6H_5Br} + Mg = \underset{\text{Phenyl magnesium bromide}}{C_6H_5\cdot Mg\cdot Br}$$

$$\underset{\text{Benzyl chloride}}{C_6H_5CH_2\cdot Cl} + Mg = \underset{\text{Benzyl magnesium chloride}}{C_6H_5\cdot CH_2\cdot Mg\cdot Cl}$$

Like the aliphatic organomagnesium halides, these have been employed with striking success in synthesis, and numerous examples of their use will be found in the following pages.

Iodine compounds containing the iodine atom in the nucleus possess the property of uniting with two atoms of chlorine to form iodochlorides, in which the iodine is trivalent. Aqueous sodium hydroxide converts these into iodoso-derivatives, the two chlorine atoms being replaced by one of oxygen.

$$\underset{\text{Iodobenzene}}{C_6H_5\cdot I} \xrightarrow{Cl_2} \underset{\text{Phenyl iodochloride}}{C_6H_5\cdot ICl_2} \xrightarrow{H_2O} \underset{\text{Iodosobenzene}}{C_6H_5\cdot I:O}$$

Iodoso-compounds are yellow amorphous substances which behave as diacid bases, *e.g.* as $C_6H_5\cdot I(OH)_2$; they combine with acids to form salts. With reducing agents, such as hydriodic acid, they lose

[1] Kenner and collaborators, *J. C. S.*, 1914, 105, 2717, and onwards. [2] K. W. Rosenmund, *Ber.*, 1923, 56, 1950.

oxygen and regenerate the iodo-compounds, a change which may also take place merely on heating (I) Oxidising agents convert iodoso- into iodoxy-compounds (II)

$$\text{I} \quad \underset{\text{Iodosobenzene}}{2C_6H_5IO} = \underset{\text{Iodoxybenzene}}{C_6H_5IO_2} + \underset{\text{Iodobenzene}}{C_6H_5I}$$

$$\text{II} \quad C_6H_5IO + O = C_6H_5IO_2$$

The iodoxy compounds do not yield salts with acids, but resemble the iodoso-derivatives in decomposing violently when heated

Chloro-, bromo-, and iodo-benzene[1] are colourless liquids of characteristic odour, which boil at 132°, 157° and 188° respectively *Hexachlorobenzene*, C_6Cl_6, is prepared by the exhaustive chlorination of benzene, and of many alkyl benzenes It is a colourless crystalline substance, which melts at 226° and boils at 326°.

Chlorotoluene, $C_6H_4Cl \cdot CH_3$, exists in three isomerides (*o*-, *m*-, and *p*-), which may be obtained from the corresponding aminotoluenes or toluidines by way of the diazo-compounds *Benzyl chloride*, $C_6H_5 \cdot CH_2Cl$, is formed by the action of chlorine on boiling toluene, it is a colourless liquid, b p 178°, which has a powerful irritant action on the eyes and nose It is used in the preparation of benzyl derivatives *Benzal chloride*, $C_6H_5 \cdot CHCl_2$, b p 207°, and *benzotrichloride*, $C_6H_5 \cdot CCl_3$, b p 213°, are formed by more prolonged action of chlorine on boiling toluene, and are utilised industrially, the former in the preparation of benzaldehyde and the latter in that of benzoic acid When the mixture of the two chlorides, as obtained by chlorination, is heated with milk of lime, it yields benzaldehyde, calcium benzoate and calcium chloride

$$\underset{\text{Benzal chloride}}{C_6H_5 \cdot CHCl_2} + Ca(OH)_2 = \underset{\text{Benzaldehyde}}{C_6H_5 \cdot CHO} + CaCl_2 + H_2O$$

$$\underset{\text{Benzotrichloride}}{2C_6H_5 \cdot CCl_3} + 4Ca(OH)_2 = \underset{\text{Calcium benzoate}}{(C_6H_5COO)_2Ca} + 3CaCl_2 + 4H_2O$$

From this mixture benzaldehyde is removed by steam distillation, and benzoic acid is then precipitated from the residual calcium benzoate by means of hydrochloric acid

V

Nitrogen Derivatives of the Aromatic Hydrocarbons

In this section, the technically valuable nitro- and amino-compounds are described first, followed by the intermediate products formed during the reduction of nitro- to amino-compounds Chief among the latter

[1] Iodobenzene can also be prepared from bromobenzene, by converting it into phenyl magnesium bromide and subsequent treatment with iodine, $C_6H_5MgBr + I_2 = C_6H_5I + MgBrI$ Bodroux, *C r*, 1913, **136**, 1350

are nitroso- and β-hydroxylamine-derivatives and azoxy-, azo- and hydrazo compounds. After these the diazo-compounds and hydrazines are treated, and finally the azo-dyes, which contain a variety of other groups in addition to nitrogen.

I.—NITRO-COMPOUNDS

Preparation.—On account of their practical value the nitro compounds are of outstanding importance. As has already been stated (p. 361), they are readily formed from aromatic hydrocarbons by the action of concentrated nitric acid:

$$C_6H_6 + HNO_3 = C_6H_5 \cdot NO_2 + H_2O$$

In a similar manner all kinds of aromatic derivatives, such as phenols, amines, aldehydes and acids, can be nitrated. The elimination of water is usually hastened by the addition of concentrated sulphuric acid to the nitric acid,[1] and the reaction may be carried out either by adding the substance to be nitrated to the mixture of acids, or by allowing nitric acid to run into a solution of the substance in sulphuric acid. The nitro-compounds can be isolated from the reaction mixture by dilution with water, in which they are generally insoluble or sparingly soluble.

A more recent method of nitration[2] makes use of liquid or gaseous nitrogen peroxide in the presence of aluminium chloride, an intermediate complex being formed, which for benzene has the composition $2AlCl_3, 3N_2O_4, 3C_6H_6$. Inorganic nitrates, such as sodium, potassium or bismuth nitrates, may also be employed for nitration.[3]

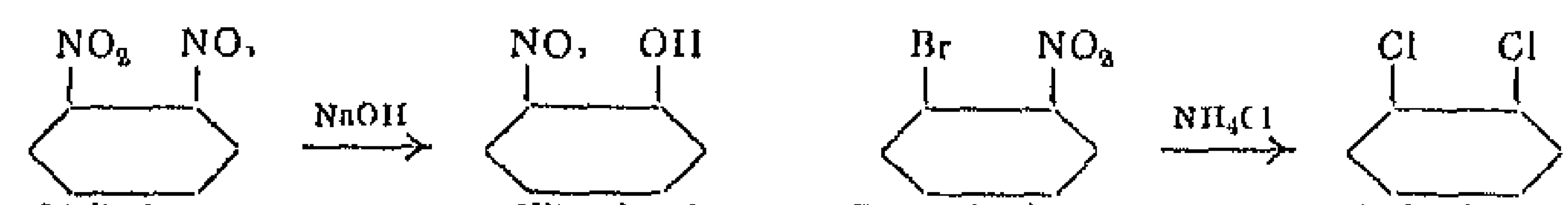
Although there is no difficulty in replacing all the hydrogen atoms in benzene with chlorine or bromine, it has not yet been found possible to effect the direct introduction of more than three nitro groups into benzene or its derivatives. In the alkyl benzenes, the more alkyl groups there are attached to the nucleus, the more readily nitration proceeds. Where only one alkyl radical is attached to the ring, the nitro group tends to assume the ortho- or para- but not the meta-position. Thus toluene yields *o*- and *p*-nitrotoluenes, but little *m*-nitrotoluene. The presence of a hydroxyl group in the nucleus also exerts a directive influence towards the *o*- and *p*-positions, *e.g.* phenol gives *o*- and *p*-nitrophenol. On the other hand, in compounds containing the radicals —CHO, —COOH, or —CN, the nitro group tends to assume the meta-position. Similarly, when one nitro group is already present, a second generally enters in the meta-position.

Properties and Reactions.—The nitro-compounds are liquids or crystalline solids, the majority of which are yellow in colour. They are only very slightly soluble in water, but in organic solvents, such

[1] A mixture of nitric acid and acetic anhydride has been found to be a very energetic nitrating agent. A. Pictet and Khotinsky, *Ber.*, 1907, 40, 1163. [2] A. Schaarschmidt, *Ber.*, 1924, 57, 2065. [3] L. Spiegel and Haymann, *Ber.*, 1926, 59, 202.

as alcohol and ether, they usually dissolve readily. Many of them are volatile in steam. Their boiling-points lie higher than those of the parent hydrocarbons. When treated with sodium or potassium alcoholates, the almost colourless trinitrobenzenes form dark red addition compounds, the constitution of which has not yet been determined.[1] In the mono-substituted derivatives the nitro group is firmly united to the nucleus and cannot be directly exchanged for other atoms or groups. In the polynitro-compounds or halogen substituted nitro compounds, on the other hand, the nitro groups are more mobile, and one of them can often be replaced by other radicals.

o-Dinitrobenzene, for example, when boiled with alkali yields *o*-nitrophenol, and *o*-bromonitrobenzene gives *o*-dichlorobenzene when heated to 320° with ammonium chloride.[2]



o-Dinitrobenzene   *o*-Nitrophenol   *o*-Bromonitrobenzene   *o*-Dichlorobenzene

Behaviour of the Nitro-compounds on Reduction

The behaviour of the aromatic nitro compounds on reduction is of great practical and theoretical interest. When reduced by purely chemical methods the final products, as in the case of the aliphatic derivatives, are amino compounds.

$$C_6H_5NO_2 + 6H = C_6H_5.NH_2 + 2H_2O$$

The reaction, however, proceeds in several stages, and intermediate products are formed which may be isolated. One of the factors greatly influencing the course of reduction is the acidity or alkalinity of the solvent during the reaction. By the reduction of nitrobenzene in acid or neutral solution, Bamberger[3] showed that the *mononuclear intermediate products*, nitrosobenzene and phenylhydroxylamine, are first formed, and that these on further reduction yield aniline.[4]

$$\underset{\text{Nitrobenzene}}{C_6H_5.NO_2} \longrightarrow \underset{\text{Nitrosobenzene}}{C_6H_5.NO} \longrightarrow \underset{\beta\text{-Phenylhydroxylamine}}{C_6H_5.NHOH} \longrightarrow \underset{\text{Aniline}}{C_6H_5.NH_2}$$

When the reduction is effected in alkaline solution, the simpler products just described tend to interact with one another to give the more complex *dinuclear intermediate products*, azoxybenzene, azobenzene and hydrazobenzene.

$$\underset{\text{Nitrobenzene}}{\begin{matrix}C_6H_5.NO_2\\ \\ C_6H_5.NO_2\end{matrix}} \longrightarrow \underset{\text{Azoxybenzene}}{\begin{matrix}C_6H_5.N{:}O\\ \| \\ C_6H_5.N\end{matrix}} \longrightarrow \underset{\text{Azobenzene}}{\begin{matrix}C_6H_5.N\\ \| \\ C_6H_5.N\end{matrix}} \longrightarrow \underset{\text{Hydrazobenzene}}{\begin{matrix}C_6H_5.NH\\ | \\ C_6H_5.NH\end{matrix}} \longrightarrow \underset{\text{Aniline}}{\begin{matrix}C_6H_5.NH_2\\ \\ C_6H_5.NH_2\end{matrix}}$$

[1] A. Hantzsch and Picton, *Ber.*, 1909, **42**, 2119. [2] J. Schmidt and Ladner, *Ber.*, 1904, **37**, 4403. [3] E. Bamberger, *Ber.*, 1894, **27**, 1550. [4] As will be seen later, the oxidation of aniline to nitrobenzene represents the reverse of the above process.

Azoxybenzene is here produced by the condensation of nitrosobenzene with phenylhydroxylamine, according to the equation

$$C_6H_5NO + C_6H_5 \cdot NHOH = C_6H_5 \cdot N_2O \cdot C_6H_5 + H_2O$$

whilst the interaction between nitrobenzene and hydrazobenzene leads to the formation of azobenzene[1]

Azobenzene is also produced from phenyl-hydroxylamine under the influence of alkali

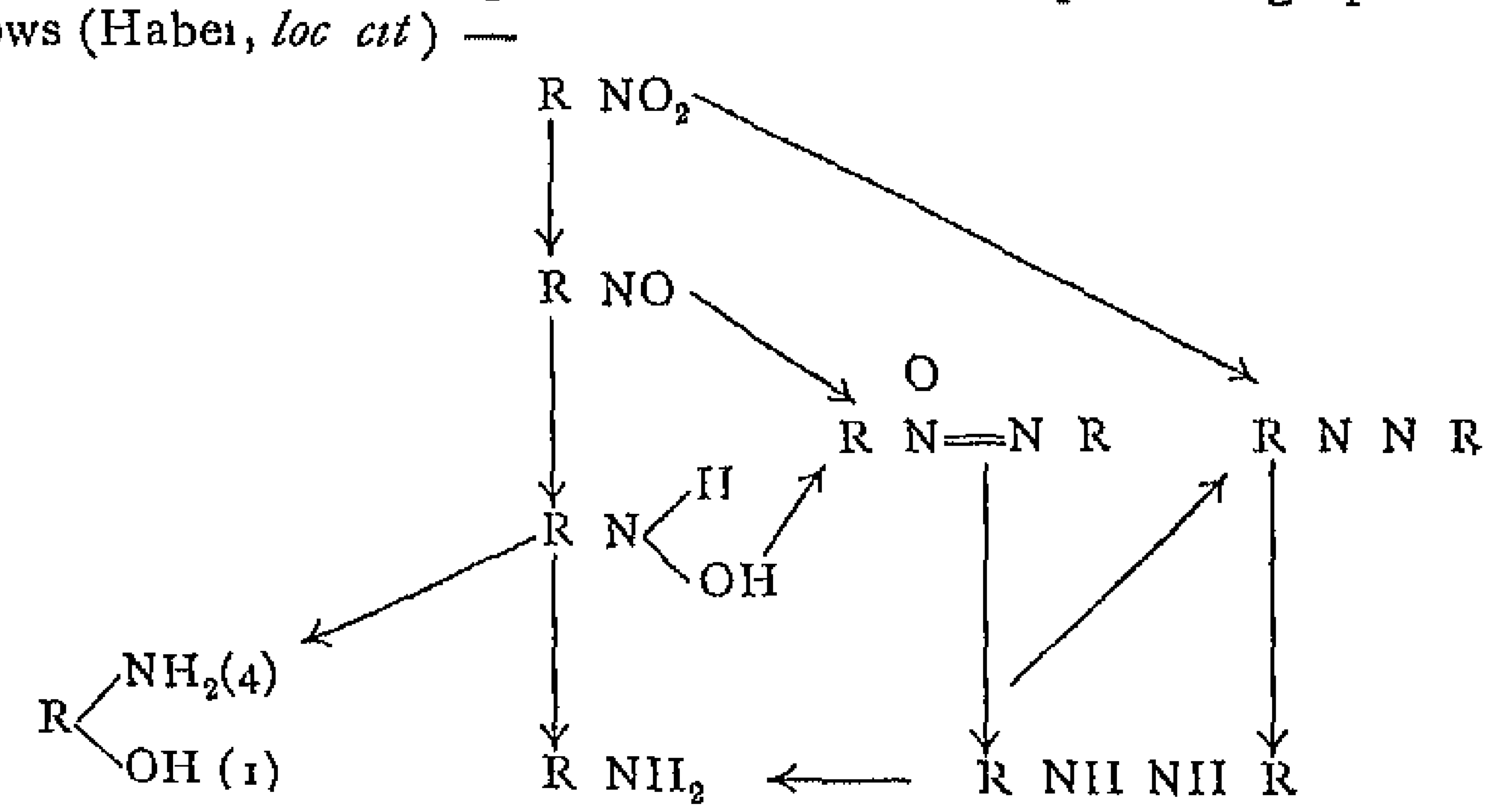
$$2C_6H_5 \cdot NHOH = C_6H_5 \cdot N_2 \cdot C_6H_5 + 2H_2O$$

The course of the electrolytic reduction of aromatic mononitro-compounds has also been carefully investigated[2] Once again employing nitrobenzene as our example, the main stages of the reduction in both alkaline and acid solution are nitrobenzene ⟶ nitrosobenzene ⟶ phenylhydroxylamine ⟶ aniline Secondary reactions, as before, play a considerable part In weakly acid solution nitrobenzene gives aniline in good yield, but in strongly acid solution *p*-aminophenol is produced, owing to the *β*-phenyl-hydroxylamine undergoing intramolecular rearrangement

$$\underset{\beta\text{ Phenylhydroxylamine}}{C_6H_5 \cdot NHOH} \longrightarrow \underset{p\text{ Aminophenol}}{HO \cdot C_6H_4 \cdot NH_2}$$

In an alkaline medium nitrosobenzene unites with *β*-phenylhydroxylamine, as described above, to form azoxybenzene, which reduces further to hydrazobenzene The latter, by atmospheric oxidation, yields a little azobenzene, and on continued reduction is converted into aniline

The various reactions taking place during the cathodic reduction of aromatic mononitro-compounds[3] have been expressed graphically as follows (Haber, *loc cit*) —



In the above scheme the electrolytic reduction processes are indicated by perpendicular and horizontal arrows, and secondary changes by inclined arrows

[1] E Bamberger, *Ber*, 1900, 33, 271 [2] Haber, *Z Elek*, 1898, 4, 511; *Z phys Ch*, 1900, 32, 271 [3] For the electrochemical reduction of aromatic dinitro and polynitro compounds, see Brand, *Ber*, 1905, 38, 4006

Description of the more Important Nitro-Derivatives of the Benzene Series

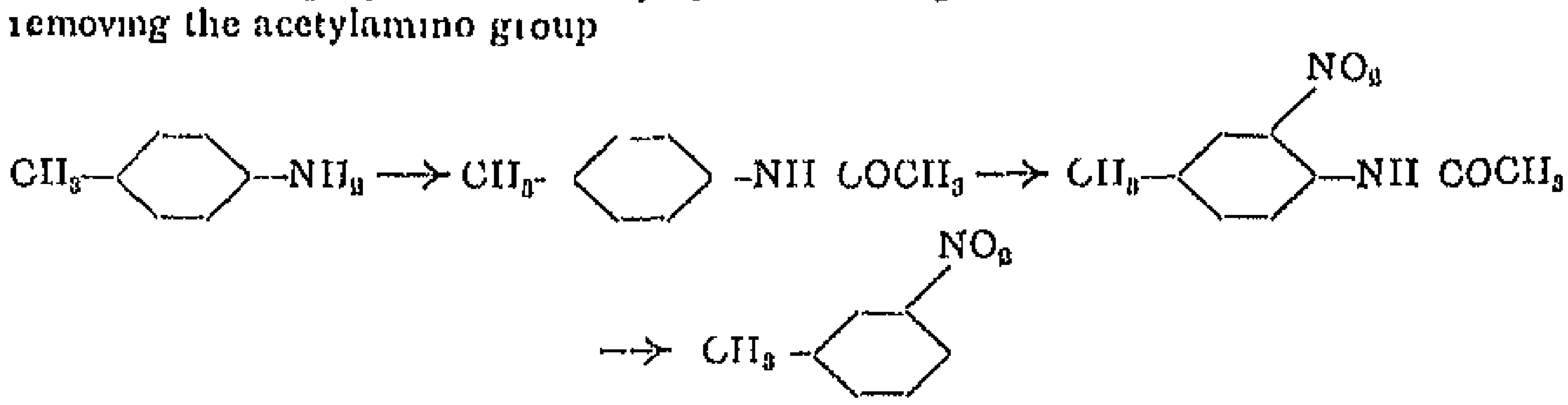
Nitrobenzene, $C_6H_5 \cdot NO_2$, *oil of mirbane*, is prepared technically in very large quantities by allowing a nitrating acid, composed of 105 parts nitric acid and 160 parts sulphuric acid, to run slowly with continuous stirring into benzene contained in cast-iron cylinders. By suitable means the temperature is maintained first at 25°, and towards the end of the reaction is allowed to rise to 70°-80°. The proportions employed are such that the nitric acid is almost completely used up, the sulphuric acid absorbing the water liberated. Nitrobenzene separates out in an upper layer above the denser acid, and is removed, washed with water and distilled in steam. A small quantity of *m*-dinitrobenzene, $C_6H_4(NO_2)_2$, remains behind. The lower layer of sulphuric acid is freed from nitric acid and organic matter, and then concentrated and used for further nitrations.

Nitrobenzene is a yellow, strongly refractive liquid, of sp. gr. 1·204 at 20°, which like benzaldehyde has a smell resembling that of bitter almonds. It boils at 208° and solidifies at 5·5°. Very dilute solutions of nitrobenzene in water have a decidedly sweet taste, and the vapour of the compound is poisonous when inhaled. Nitrobenzene is chiefly used in industry for the preparation of aniline, and also in the manufacture of perfumes and perfumed soaps.

Dinitrobenzenes, $C_6H_4(NO_2)_2$. The nitration of benzene at higher temperatures yields *m*-*dinitrobenzene*, m.p. 90°, as chief product, together with small amounts of the *o*-compound (m.p. 116°) and *p*-compound (m.p. 172°). The first of these serves for the production of *m*-nitraniline and *m*-phenylene diamine, which are used in the dye industry, and is also a component of certain explosives.

Sym. or 1 : 3 : 5-Trinitrobenzene, $C_6H_3(NO_2)_3$, m.p. 121°, is formed by heating benzene to 140° with a mixture of nitric and fuming sulphuric acids.

Nitrotoluene, $CH_3 \cdot C_6H_4 \cdot NO_2$. Toluene on nitration yields a mixture of *o*- and *p*-nitrotoluenes containing a little of the *m*-compound. These can be separated by fractional distillation. *o*-*Nitrotoluene*, b.p. 218°, gives *o*-nitrobenzaldehyde on oxidation and is also used in the preparation of *o*-nitrobenzyl chloride and *o*-toluidine. It exists in two isomeric forms,[1] a labile *α*-modification, m.p. −9·4°, and a stable *β*-modification, m.p. −3·6°. *p*-*Nitrotoluene*, b.p. 230° and m.p. 54°, is converted by the action of fuming sulphuric acid into *p*-nitrotoluene-*o*-sulphonic acid, which is used in the preparation of the dyestuff Direct Yellow. Pure *m*-*nitrotoluene*, m.p. 16°, b.p. 230°, is best prepared indirectly by nitration of *p*-acetotoluidide and subsequently removing the acetylamino group.



[1] Knoevenagel, *Ber.*, 1907, 40, 508.

2 4 6 **Trinitro** *tert* **butyl toluene**, $C_6H[NO_2, NO_2, NO_2, CH_3, C(CH_3)_3 = 2\ 4\ 6\ 1\ 3]$, m p 97, smells powerfully of musk and is brought on to the market as *artificial musk* (mixed with 80 per cent acetanilide) It is obtained by the nitration of butyl toluene (prepared from isobutyl chloride, toluene, and aluminium chloride)

II — AMINO DERIVATIVES OF BENZENE

The aromatic amines may be derived theoretically from ammonia in the same manner as the aliphatic amines In the true aromatic derivatives the nitrogen is attached directly to the benzene nucleus, as in $C_6H_5\ NH_2$ and $NH_2\ C_6H_4\ CH_3$ When, however, the amino group is linked to a carbon atom of the side chain in an alkyl benzene, as in the case of $C_6H_5\ CH_2\ NH_2$, we are dealing with a substituted aliphatic amine, with properties like those of the alkyl amines The true aromatic amines undergo many of the reactions given by the fatty amines (pp 160 *et seq*) but differ from the latter in a number of points For example, the aromatic derivatives are weaker bases than those of the aliphatic series, owing to the acidic character of the phenyl group In addition, primary and tertiary aromatic amines differ from the corresponding aliphatic compounds in their behaviour towards nitrous acid

1 Primary Monamines

Methods of Formation —The primary aromatic amines are almost always prepared by reducing the corresponding nitro-compounds

$$C_6H_5NO_2 + 6H = C_6H_5NH_2 + 2H_2O$$

This can be effected in various ways, such as by the use of zinc and hydrochloric acid, tin or stannous chloride and hydrochloric acid, iron and hydrochloric acid, alcoholic ammonium sulphide, or by electrochemical methods The intermediate products which are formed under different conditions have already been described in detail in the foregoing pages

Amines may be obtained from phenols by heating them to 150° with the double compound of zinc chloride and ammonia, $(ZnCl_2, NH_3)$, *e g*, $C_6H_5OH + NH_3 = C_6H_5NH_2 + H_2O$ The substitution of an amino-group for a phenolic hydroxyl group or a halogen atom attached to a benzene nucleus takes place more readily when nitro groups are also present in the compounds Sulphonic acids, in many cases, can be transformed into amines by heating with sodamide [1]

The exchange of the —COOH group of aromatic carboxylic acids for the amino group may be effected in the same manner as with the aliphatic acids

Among other methods of preparing amines may be mentioned one discovered by A W Hofmann When aniline is heated to a high temperature with alkyl halides, an N-alkyl derivative is first formed, which changes by intramolecular rearrangement into a mixture of nuclear-substituted anilines The procedure recommended by Hofmann is to start with the hydrochlorides of secondary or tertiary fatty-

[1] F Sachs, *Ber*, 1906, 39, 3006

aromatic amines, or the quaternary ammonium salts, and heat in closed vessels at a temperature of 250° to 300°. Ethylaniline hydrochloride, for example, first yields free ethyl chloride, and this then brings about substitution in the benzene nucleus:

$$\begin{matrix} C_6H_5 \\ C_2H_5 \end{matrix}\!\!>NH.HCl \longrightarrow C_6H_5.NH_2+C_2H_5.Cl \longrightarrow \begin{matrix} C_6H_4.NH_2,HCl \\ | \\ C_2H_5 \end{matrix}$$

By this means Hofmann prepared an aniline derivative in which all five hydrogen atoms of the ring were replaced by methyl groups:

$$(CH_3)_3C_6H_2.N(CH_3)_2,HI \longrightarrow (CH_3)_5C_6.NH_2,HI$$

It should be noted that this reaction is not only of scientific interest,[1] but is also of great practical value. It is employed on the technical scale for the production of the aniline homologues required in the dyestuff industry.

Properties and Reactions.—The primary monamino-compounds are colourless liquids or solids, which are volatile with steam and can be distilled without decomposition. As already mentioned, they are weak bases which do not give an alkaline reaction. With the entrance of electronegative groups such as Cl and NO_2 into the nucleus, the basic character becomes still weaker, and the salts of these substituted anilines are either dissociated with water or incapable of existence. From the chemical point of view, the primary aromatic amines resemble the fatty compounds in their behaviour towards alkylating agents, acid chlorides, aldehydes and chloroform (see p. 124). They differ mainly in their reaction with nitrous acid, which in acid solution converts them into diazo-compounds. In the amino-benzenes, the nuclear hydrogen is far more readily substituted than in benzene itself, and in the same way the amines are much more susceptible to oxidation than the hydrocarbons. The various products obtained by the above reactions are described in detail under aniline.

According to conditions, bromine may react with aromatic amines at the ordinary temperature to form substitution or addition compounds. A study of this reaction has revealed a number of interesting regularities in connection with substitution.[2]

Aniline and its Derivatives

Aniline, *phenylamine*, $C_6H_5.NH_2$, is prepared technically from nitrobenzene. The latter is mixed with a little water in a cast-iron vessel provided with stirring apparatus and a reflux condenser. Steam is led in to warm the mixture, to which iron filings and hydrochloric

[1] A similar *migration of alkyl groups* has been observed with derivatives of other cyclic bases, such as pyridine, pyrazine, pyrrole and pyrazole. [2] See K. Fries, *Ann.*, 1906, 346, 128.

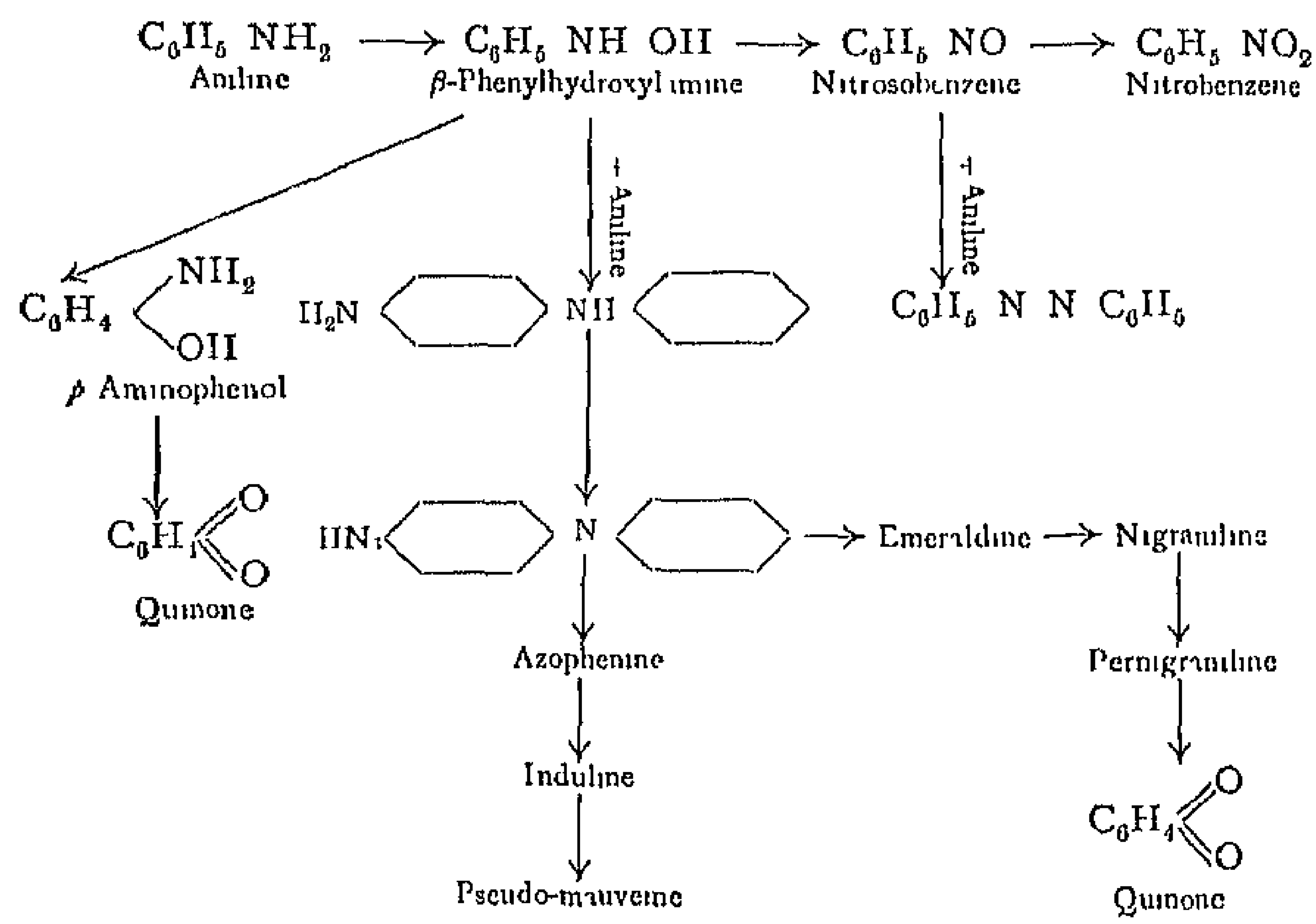
acid are then added Only a small proportion (about $\frac{1}{10}$) of the amount of acid required by the equation is needed in actual practice[1]

$$C_6H_5NO_2 + 2Fe + 6HCl = C_6H_5NH_2 + 2FeCl_3 + 2H_2O$$

At the end of the reaction milk of lime is added, in order to decompose the aniline hydrochloride formed, and the free aniline is distilled over in steam and fractionated *in vacuo* For the intermediate stages in this reduction see p 378

In the pure state aniline is a colourless strongly refractive liquid of sp gr 1 024 at 16°, which boils at 189° and solidifies at −8° It is only sparingly soluble in water and is poisonous

Aniline is easily attacked by oxidising agents, the products obtained depending very much on the conditions of experiment They may be conveniently classified as *mononuclear oxidation products*, such as phenylhydroxylamine, nitrobenzene and quinone, *dinuclear products*, such as azobenzene, azoxybenzene and quinonediimine, and those which may be termed *polynuclear*, such as emeraldine and aniline black, which result from further chain formation and secondary reactions[2] The genetic connection between these various products of reaction is summarised in the following table,[3] in which the series in the first line, connected by horizontal arrows, is exactly the reverse of that given on p 378 for the reduction of nitrobenzene



[1] For an explanation of this, see A Wohl, *Ber*, 1894, **27**, 1436, 1815 The reduction may also be effected by means of iron and neutral salts (*e g* NaCl) in aqueous solution, R E Lyons and L T Smith, *Ber*, 1927, **60**, 173 [2] Willstätter, *Ber*, 1907, **40**, 2665, 1909, **42**, 2147, 4118 [3] S Goldschmidt, *Ber*, 1920, **53**, 28

An exceedingly delicate test for the presence of aniline consists in treating it in aqueous solution with a solution of bleaching powder (Runge), when a deep violet coloration is produced, which changes rapidly to a dirty red tint. Another characteristic reaction of aniline is the formation of a deep blue or black colour (aniline black) when potassium bichromate is added to a solution of the base in sulphuric acid.

Halogens readily yield substitution derivatives with aniline. Bromine, for example, converts it into 2 : 4 : 6 *tribromo-aniline*, a reaction which may be used for the quantitative estimation of aniline. By interaction with sulphur, aniline forms a diamino-diphenyl sulphide, $(NH_2 \cdot C_6H_4)_2S$, m.p. 108°, in which the amino groups occupy the *p* positions to the sulphur atom.

The most important salt of aniline is the readily soluble hydrochloride, $C_6H_5 \cdot NH_2, HCl$, known technically as *aniline salt*. The sulphate $(C_6H_5 \cdot NH_2)_2H_2SO_4$ is only sparingly soluble in water.

Aniline reacts with aromatic aldehydes with elimination of water to form *Schiff's* bases or *anils*.

$$C_6H_5 \cdot CHO + H_2N \cdot C_6H_5 = \underbrace{C_6H_5 \cdot CH : N \cdot C_6H_5}_{\text{Benzylidene aniline}} + H_2O$$

If the hydrogen atoms of the amino-group in aniline are replaced by organic acid radicals, compounds termed *anilides* are produced. These can be prepared by heating aniline salts with the required organic acids, or by the interaction of aniline and an acid chloride or ester. The best known example of this class is acetanilide.

Acetanilide, $C_6H_5 \cdot NH \cdot CO \cdot CH_3$, may be prepared by heating acetic acid with aniline or aniline acetate.

$$CH_3COOH + NH_2 \cdot C_6H_5 = CH_3CO \cdot NH \cdot C_6H_5 + H_2O$$

It melts at 112°, boils at 304°, and is only very sparingly soluble in cold water, from which it crystallises in small white plates. Acetanilide is employed in medicine as a febrifuge under the name of *antifebrin*.

Nitric acid reacts vigorously with aniline, converting it into resinous products. Hence, in order to obtain mono- and dinitro-derivatives the amino group must first be protected. This can be done either by acetylating the aniline before nitration, or by nitrating it with a mixture of nitric acid and much sulphuric acid. In the latter case all three isomeric mono-nitro compounds are formed together, viz., *o-nitraniline*, m.p. 71°, *m-nitraniline*, m.p. 114°, and *p-nitraniline*, m.p. 147°, whereas when the aniline is first acetylated the *p*-nitro compound is the chief product.[1] These nitranilines can also be prepared by the partial reduction of the corresponding dinitrobenzenes by means of ammonium sulphide.

The entrance of the nitro group into the molecule considerably weakens the basic character of aniline. This is illustrated by the following lecture experiment devised by J. Thiele, which also offers a characteristic example of the influence of substituents in the benzene ring. The three finely powdered nitranilines are dissolved in a little concentrated sulphuric acid contained in three test tubes, and the colourless solutions poured into water. The greater part of the *o*-nitraniline is precipitated with the development of a strong yellow coloration, the *p*-nitraniline remains in solution but is coloured distinctly yellow, and the *m*-nitraniline is neither precipitated nor

[1] A. F. Holleman, *Ber.*, 1911, 44, 704.

coloured. From this it may be concluded that the effect of the nitro group on the basic properties of the amino group is most marked in the *o* position, somewhat less in the *p* and least of all in the *m* position.

Carbonic Acid Derivatives of Aniline

The anilides of carbonic acid correspond to the carbamides and may be obtained in a similar manner to these (see p. 331).

Phenyl urethane, $C_6H_5\cdot NH\cdot CO\cdot OC_2H_5$, can be prepared by the action of aniline on chlorocarbonic ester. *Carbanilide* or *sym. diphenyl urea*, $(C_6H_5\cdot NH)_2CO$, m.p. 235°, and *phenyl urea*, $C_6H_5\cdot NH\cdot CO\cdot NH_2$, m.p. 144°, are obtained by special methods, *e.g.* from aniline sulphate and potassium cyanate, or by heating aniline with urea. **Phenyl isocyanate**, $C_6H_5\cdot N{:}C{:}O$, b.p. 166°, can be prepared by treating aniline or its hydrochloride with phosgene, or by distilling phenyl urethane with phosphorus pentoxide. It is a colourless liquid, the vapour of which has a lachrymatory action. Phenyl isocyanate has often been employed in the examination of tautomeric compounds, particularly for showing the presence of a hydroxyl group. The interaction of equimolecular quantities of phenyl isocyanate and a hydroxy derivative leads to the formation of a *phenyl carbamic ester*, according to the equation

$$R\cdot OH + \overset{O}{C}{:}N\cdot C_6H_5 = RO{-}\overset{O}{C}{-}NH\cdot C_6H_5$$

Later research, however, has shown that this substance is not a reliable reagent for the hydroxyl group.[1] Under the influence of various substances phenyl isocyanate polymerises to triphenyl isocyanate, m.p. 274°. In contact with water it yields diphenyl urea.

Thiocarbanilide, diphenyl thiourea, $(C_6H_5NH)_2CS$, is prepared by boiling aniline with carbon disulphide:

$$CS_2 + 2H_2NC_6H_5 = H_2S + CS(NHC_6H_5)_2$$

It is obtained in the form of colourless plates, m.p. 154°. When heated with concentrated hydrochloric acid it decomposes into aniline and phenyl isothiocyanate (phenyl mustard oil), $C_6H_5\cdot N{:}C{:}S$, a colourless liquid of pungent smell.

Monamino Derivatives of Toluene

Toluidines, $CH_3\cdot C_6H_4\cdot NH_2$.—The ortho and para derivatives are obtained by reducing the corresponding nitrotoluenes with iron and hydrochloric acid, and are employed in the manufacture of azo- and triphenyl methane dyestuffs. *o*-Toluidine is a liquid, b.p. 197°, and *p*-toluidine a solid which melts at 45° and boils at 198°. *m*-Toluidine can be prepared from *m*-nitrotoluene (obtained by indirect methods, see p. 379) and is a liquid, b.p. 199°.

Benzylamine, $C_6H_5\cdot CH_2\cdot NH_2$, b.p. 183°, which may be regarded as a phenyl-substituted methylamine, is formed by the methods described under aliphatic amines, *e.g.*, by heating benzyl chloride, $C_6H_5\cdot CH_2Cl$, with ammonia, or by the reduction of phenyl nitromethane, $C_6H_5\cdot CH_2\cdot NO_2$. It is a colourless liquid, and in its chemical properties resembles methylamine. It dissolves in water to give a strongly alkaline solution and yields no diazo-compound with nitrous acid.

[1] See Dieckmann, Hoppe and Stein, *Ber.*, 1904, 37, 4627; Michael, *Ber.*, 1905, 38, 22; H. Goldschmidt, *Ber.*, 38, 1896.

2 Secondary Monamines

Purely aromatic secondary amines may be prepared by heating the primary bases with their hydrochloric acid salts For example, by heating aniline with aniline hydrochloride at 220° to 230° in an autoclave, **diphenylamine**, $(C_6H_5)_2NH$, is formed

$$C_6H_5NH_2, HCl + H_2NC_6H_5 = HN(C_6H_5)_2 + NH_4Cl$$

Another method of preparing compounds of this type is by the action of bromobenzene on primary aromatic amines, in the presence of a trace of cuprous iodide as catalyst[1] Diphenylamine is a colourless crystalline substance, m p 54° and b p 310°, which is used in the preparation of diamino-diphenylamine and azo-dyes Its basic properties are so weak that its salts are decomposed with water On the other hand, the hydrogen of the imino group is replaceable by metals With nitrous acid it yields diphenylnitrosamine, $(C_6H_5)_2N \cdot NO$

Diphenylamine is rapidly attacked by oxidising agents, yielding a product which gives an intense blue coloration with concentrated sulphuric acid Hence it is employed for the qualitative detection of nitric and nitrous acids This behaviour is due to the formation of tetraphenyl hydrazine, which gives the above striking colour reaction with concentrated sulphuric acid[2]

$$\underset{\text{Diphenylamine}}{2(C_6H_5)_2NH} \xrightarrow{O} \underset{\text{Tetraphenyl hydrazine}}{(C_6H_5)_2N-N(C_6H_5)_2} + H_2O$$

Secondary *mixed aromatic amines* or phenyl-alkylamines may be prepared from alkyl iodides and the acetyl derivatives of primary aromatic bases[3] **Methylaniline**, for example, is formed in this manner by the action of methyl iodide on the sodium salt of acetanilide, and subsequent removal of the acetyl group by hydrolysis

$$C_6H_5N{<}^{COCH_3}_{Na} \xrightarrow{ICH_3} C_6H_5N{<}^{COCH_3}_{CH_3} \xrightarrow{HCl} C_6H_5N{<}^{H}_{CH_3}$$

The secondary mixed aromatic amines are stronger bases than the purely aromatic compounds When treated with nitrous acid they yield nitroso derivatives, $C_6H_5N(R) \cdot NO$, which with weak reducing agents are converted into hydrazines, $C_6H_5N(R) \cdot NH_2$, and on energetic reduction regenerate the original secondary amine

3 Tertiary Monamines

In this case also a distinction must be drawn between compounds of purely aromatic and those of mixed aliphatic-aromatic nature A point of outstanding interest is the behaviour of phenyl dialkylamines

[1] I Goldberg, *Ber*, 1907, 40, 4541 [2] Wieland, *Ber*, 1906, 39, 1499 F Weitz and H W Schwechten, *Ber*, 1927, 60, 1203 [3] For details of preparation from aromatic amines and alkyl bromide, see W J Hickinbottom, *J C S*, 1930, 992

towards nitrous acid Whereas tertiary aliphatic amines do not react with nitrous acid at all, mixed amines of the above type are transformed by this reagent into *p*-nitroso-compounds (see below) A small proportion of a nitro derivative is also formed as a by-product in this reaction

Tertiary phenylamines either fail to react with nitrous acid or undergo nitration in the nucleus

Triphenylamine, $(C_6H_5)_3N$, can be obtained by the action of bromobenzene on dipotassium aniline, $C_6H_5NK_2 + 2C_6H_5Br = (C_6H_5)_3N + 2KBr$ It melts at 127° and forms no salts with acids

Dimethylaniline, $C_6H_5N(CH_3)_2$, is formed by the methylation of aniline, and is prepared industrially by heating aniline hydrochloride with methyl acohol in autoclaves

$$C_6H_5NH_2, HCl + 2CH_3OH = C_6H_5 N(CH_3)_2, HCl + 2H_2O$$

The resulting hydrochloride of dimethylaniline is treated with milk of lime, and the free base removed by distillation in steam It is an oil of peculiar smell, boiling at 192° With dry hydrogen chloride the base yields a mono- and a di hydrochloride, both of which readily lose hydrochloric acid[1] A number of the characteristic reactions of dimethylaniline depend on the extraordinary mobility of the hydrogen atom in the para-position Thus with nitrous acid it gives *p* **nitroso dimethylaniline**, $(NO)C_6H_4 N(CH_3)_2$, crystallising in green leaves or plates, m p 85° The hydrochloride of the nitroso-base crystallises in yellow needles, melting at 177° When *p* nitroso-dimethylaniline is reduced with zinc dust it yields *p*-amino dimethylaniline, $NH_2 C_6H_4 N(CH_3)_2$, which, like the nitroso-compound, is used in the manufacture of numerous dyes

Dimethylaniline condenses with aldehydes in such a manner that the para hydrogen atoms of two molecules of the base unite with the aldehydic oxygen to form water

$$\underset{\text{Formaldehyde}}{H\,CH\,O} + \underset{\text{Dimethylaniline}}{2C_6H_5N(CH_3)_2} = \underset{\substack{\text{Tetramethyl diamino}\\\text{diphenylmethane}}}{H_2C\begin{cases}\overset{1}{C_6}H_4\overset{4}{N}(CH_3)_2\\ \underset{1}{C_6}H_4\underset{4}{N}(CH_3)_2\end{cases}} + H_2O$$

Acid chlorides react in a similar way,

$$\underset{\text{Phosgene}}{COCl_2} + \underset{\text{Dimethylaniline}}{2C_6H_5N(CH_3)_2} = \underset{\text{Michler's ketone}}{CO\begin{cases}\overset{1}{C_6}H_4\ \overset{4}{N}(CH_3)_2\\ \underset{1}{C_6}H_4\ \underset{4}{N}(CH_3)_2\end{cases}} + 2HCl$$

[1] R Scholl and Escales, *Ber*, 1897, 30, 3134

When treated with an aqueous solution of hydrogen peroxide, dimethylaniline takes up an atom of oxygen to form a product of the formula $\begin{array}{c} C_6H_5 \cdot N(CH_3)_2 \\ \| \\ O \end{array}$ known as *dimethylaniline oxide*, from which oxygen can readily be removed to give the original base.

This behaviour towards hydrogen peroxide is peculiar to all aromatic amines of the type $Ar \cdot N(Alk)_2$.

4. Diamines and Polyamines

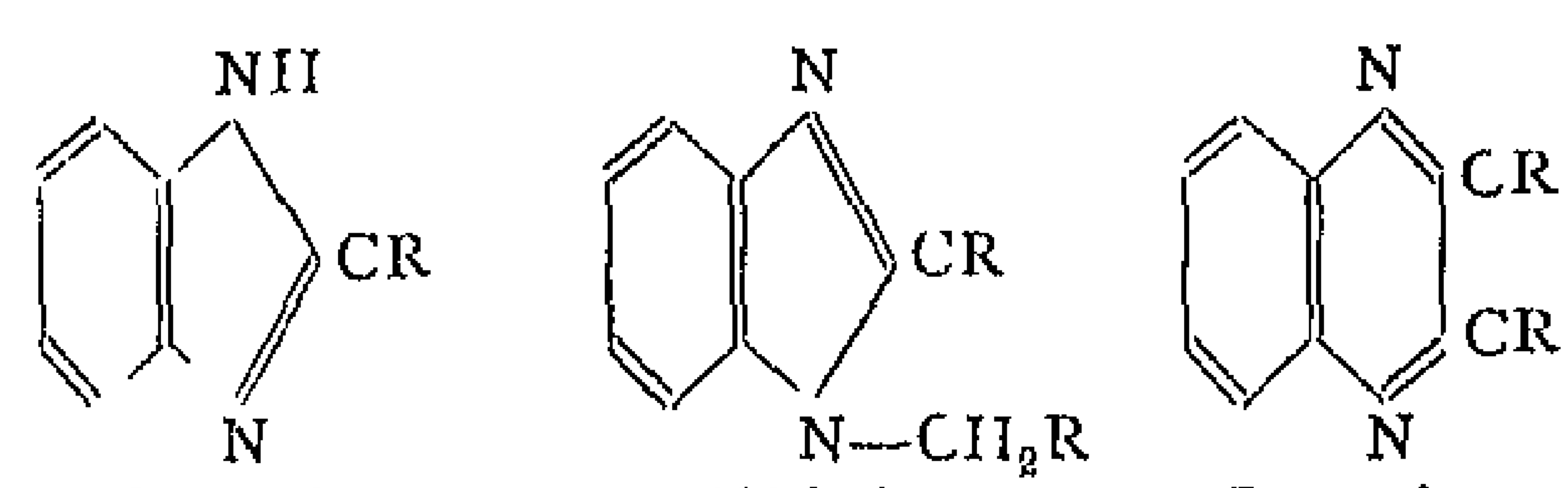
Aromatic diamines may be prepared by the reduction of the corresponding dinitro-, nitroamino-, or aminoazo compounds.

For example, m-*phenylene diamine*, $C_6H_4(NH_2)_2$, m.p. 63° and b.p. 287°, is obtained by the reduction of *m*-dinitrobenzene with zinc dust and caustic soda, and o-*phenylene diamine*, m.p. 102° and b.p. 252°, in a similar manner from *o*-nitraniline. p-*Phenylene diamine*, m.p. 147° and b.p. 267°, is prepared by reducing aminoazobenzene with tin and hydrochloric acid:

$$C_6H_5 \cdot N:N \cdot C_6H_4 \cdot NH_2 + 4H = C_6H_5 \cdot NH_2 + H_2N \cdot C_6H_4 \cdot NH_2$$

The diamines are solid compounds of strong basic properties. Their reactions differ according to the positions of the amino-groups.

o-**Diamines** are distinguished by the ease with which they condense with a variety of other compounds to form cyclic derivatives. Thus when heated with organic acids they yield iminazoles, with aldehydes they yield aldehydines, and with 1:2-diketones they yield quinoxalines.



Iminazoles Aldehydines Quinoxalines

The quinoxaline reaction[1] is useful as a qualitative test for *o*-diamines as well as for 1:2-diketones.

m-**Diamines**, when treated with nitrous acid, give brown dyes—aminoazo-compounds—produced by the condensation of several molecules of the diamine (*Bismarck brown* reaction). The *p*-substituted *m*-**diamines** do not give this colour test.

In neutral or dilute mineral acid solution *m*-diamines may be coupled with diazotised aniline to form diaminoazo-compounds known as *chrysoidines*.

The most important reactions of the *p*-**diamines** are the following. With oxidising agents, *e.g.*, when boiled with manganese dioxide

[1] O. Hinsberg, *Ann.*, 1887, 237, 327, 342.

and sulphuric acid, they readily pass into quinones, which may be recognised by their penetrating odour

$$\underset{p\text{ Phenylene diamine}}{C_6H_4(NH_2)_2} + H_2O + O = \underset{\text{Quinone}}{C_6H_4O_2} + 2NH_3$$

By the action of ferric chloride on *p* diamines in the presence of hydrogen sulphide, there are formed blue, violet, or crimson red dyestuffs, which contain sulphur Mixtures of *p*-diamines with phenols yield on oxidation dark blue *indophenol* dyestuffs Similarly the oxidation of mixtures of *p*-diamines and primary monamines at the ordinary temperature leads to the formation of highly coloured *indamines*, and at higher temperatures of *safranines*

Amines containing three or more amino-groups in the nucleus very readily undergo oxidation, and their instability increases with the number of such groups present

III —NITROSO- AND β-HYDROXYLAMINE DERIVATIVES

Mononitroso derivatives of the aromatic hydrocarbons are obtained, in general, by the action of certain oxidising agents (cold monopersulphuric acid, or potassium bichromate and sulphuric acid) on the corresponding amino compounds Ar NH_2→Ar NH OH→Ar NO Like the aliphatic nitroso derivatives (see p 154), they are very volatile and exist in different molecular states The solid aromatic nitroso-compounds are colourless and bimolecular, but in solution, or when fused, the great majority of them assume a blue or green colour and give molecular weights corresponding to the monomolecular formula Ar NO On further oxidation the nitroso compounds readily pass into nitro-compounds, and on reduction they yield amino-compounds

The typical aromatic representative of this class, **nitrosobenzene,** C_6H_5 NO, is obtained by oxidising β phenylhydroxylamine with potassium bichromate and sulphuric acid It is also formed when aniline is oxidised (*a*) in sulphuric acid solution with potassium permanganate, in the presence of a little formaldehyde, (*b*) with monopersulphuric acid (*Caro*) It crystallises in colourless volatile needles, m p 68°, and possesses a powerful characteristic smell In the molten state or in solution it is emerald green in colour It is readily oxidised to nitrobenzene or reduced to aniline Nitrosobenzene condenses with aniline to form azobenzene, and with β-phenyl hydroxylamine to form azoxybenzene (see p 378)

β-Arylhydroxylamines are prepared by reducing aromatic nitro-compounds with neutral reagents such as zinc dust and ammonium chloride solution, or ammonium sulphide They are also obtained by electrochemical reduction, in which case a cathode solution of acetic acid and sodium acetate dissolved in water or other solvent is

best employed.[1] They readily reduce ammoniacal silver solutions and Fehling's solution, and when dissolved in water rapidly take up oxygen from the air, particularly in the presence of alkali. Those β-aryl-hydroxylamines in which the *p*-hydrogen atom is not substituted are transformed by sulphuric acid into the isomeric *p*-amino-phenols (see below).

β-Phenyl-hydroxylamine, $C_6H_5 \cdot NHOH$, is obtained by reducing nitrobenzene by the above methods. It is a white crystalline compound, m.p. 81°. The powdered substance induces violent sneezing. Atmospheric oxygen converts it into azoxybenzene, and with more energetic oxidising agents it yields nitrosobenzene. It reduces Fehling's solution and ammoniacal silver nitrate, even in the cold. With acids it combines to form salts, and when warmed with mineral acids is readily isomerised to *p*-aminophenol.

$$C_6H_5 \cdot NH \cdot OH \longrightarrow HO \cdot C_6H_4 \cdot NH_2$$

Nitrous acid converts it into a nitroso derivative, $C_6H_5N(NO)OH$. This *nitrosophenyl-hydroxylamine* is more conveniently obtained by the action of nitric oxide on an ethereal solution of phenyl magnesium bromide:

$$NO \longrightarrow O:N \cdot N:O \longrightarrow O:N \cdot N\begin{matrix} \diagup OMgBr \\ \diagdown C_6H_5 \end{matrix} \longrightarrow O:N \cdot N\begin{matrix} \diagup OH \\ \diagdown C_6H_5 \end{matrix}$$

Diphenyl hydroxylamine,[2] $(C_6H_5)_2N \cdot OH$, is prepared by treating nitrosobenzene with phenyl magnesium bromide:

$$C_6H_5 \cdot NO + C_6H_5 \cdot MgBr \xrightarrow{+H_2O} (C_6H_5)_2N \cdot OH + MgBrOH$$

It is a beautifully crystalline compound which melts with decomposition at 60°, and is of interest in connection with the discovery of divalent nitrogen derivatives.

Nitrogen diphenyl, $(C_6H_5)_2N$, and other diaryl derivatives of divalent nitrogen, are formed as a result of the dissociation of tetra-aryl hydrazines.[3] Nitrogen diphenyl bears the same relationship to diphenyl-hydroxylamine as nitric oxide to nitrous acid:

$$\begin{matrix} (C_6H_5)_2N & \qquad (C_6H_5)_2N \cdot OH & \qquad (C_6H_5)_2N:O \\ O:N & \qquad O:N \cdot OH & \qquad O:N:O \end{matrix}$$

The presence of nitrogen diphenyl in a solution of tetraphenyl hydrazine can be detected by its unsaturated properties. When, for example, nitric oxide is passed into a solution of the hydrazine in toluene at 90° diphenyl nitrosamine is formed, produced by union of the two divalent nitrogen groups:

$$(C_6H_5)_2N + NO \longrightarrow (C_6H_5)_2N \cdot NO$$

The dissociation of tetraphenyl hydrazine into the free radical $(C_6H_5)_2N$ is exactly analogous to the formation of triphenyl methyl from hexaphenyl ethane, which will be discussed later:

$$(C_6H_5)_2N \cdot N(C_6H_5)_2 \longrightarrow 2(C_6H_5)_2N$$
$$(C_6H_5)_3C \cdot C(C_6H_5)_3 \longrightarrow 2(C_6H_5)_3C$$

[1] Haber, *Z. Elek.*, 1897-98, 4, 506; 5, 77. K. Brand, *Ber.*, 1905, 38, 3076. [2] H. Wieland, *Ber.*, 1912, 45, 494. [3] H. Wieland, *Ann.*, 1911, 381, 201; 1912, 392, 156; 1913, 401, 233; *Ber.*, 1912, 45, 2600.

Another compound which tends to dissociate in solution into a derivative of divalent nitrogen is *hexaphenyl tetrazane*.[1] In the solid state this is monomolecular, but in solution it largely exists as *triphenylhydrazyl*.

$$(C_6H_5)_2N-\underset{H_5C_6}{\underset{|}{N}}-\underset{C_6H_5}{\underset{|}{N}}-N(C_6H_5)_2 \rightleftarrows 2(C_6H_5)_2N-\underset{C_6H_5}{\underset{|}{N}}-$$

Diphenyl nitric oxide,[2] $(C_6H_5)_2N{:}O$, is obtained from diphenyl hydroxylamine by oxidation with silver oxide. $(C_6H_5)_2N{\cdot}OH \longrightarrow (C_6H_5)_2N{:}O$. It is an analogue of nitrogen dioxide (see above) from which it is derived by the replacement of an oxygen atom by two benzene residues. It crystallises in deep red needles, m.p. 62°, and in many ways resembles NO_2. Like the latter it shows a characteristic band spectrum, and its colour in solution resembles that of gaseous NO_2, but is of a deeper red. It unites with other radicals such as nitric oxide, nitrogen dioxide and triphenyl methyl. With NO it forms $(C_6H_5)_2N(:O){\cdot}NO$, which then undergoes intramolecular rearrangement to give *p*-nitro-diphenylamine, $O_2N{\cdot}C_6H_4{\cdot}NH{\cdot}C_6H_5$. The first stage of this reaction is comparable to the formation of N_2O_3 from NO and NO_2.

IV.—AZOXY-, AZO- AND HYDRAZO COMPOUNDS

The azoxy compounds are generally prepared by treating nitro derivatives with sodium methoxide or sodium ethoxide; sodium amalgam, or magnesium and ammonium chloride solution, can also be employed as the reducing agent. They are yellow or red in colour, crystallise well, and on further reduction yield azo-, hydrazo- and amino compounds. With moderately warm concentrated sulphuric acid they isomerise to *hydroxy azo compounds*.

Azoxybenzene, $C_6H_5{\cdot}\overset{O}{N{:}N}{\cdot}C_6H_5$, is best prepared by boiling nitrobenzene with a methyl alcoholic solution of sodium methoxide.

$$4C_6H_5{\cdot}NO_2 + 3CH_3{\cdot}ONa = 2C_6H_5{\cdot}\overset{O}{N{:}N}{\cdot}C_6H_5 + 3\underset{\text{Sodium formate}}{H{\cdot}COONa} + 3H_2O$$

It forms pale yellow crystals, m.p. 36°. When warmed with concentrated sulphuric acid it isomerises into *p*-hydroxy-azobenzene.[3]

$$C_6H_5{\cdot}\overset{O}{N{:}N}{\cdot}C_6H_5 = C_6H_5{\cdot}N{:}N{\cdot}C_6H_4{\cdot}OH$$

Azoxy compounds were formerly believed to possess the symmetrical structure, *e.g.* $C_6H_5{\cdot}N\overset{O}{\diagup\diagdown}N{\cdot}C_6H_5$. An unsymmetrical azo compound, however, was shown by Angeli to give rise in some instances to two isomeric azoxy compounds. The symmetrical formula has therefore been abandoned. Spectroscopic observations[4]

$$C_6H_5{\cdot}N{:}N{\cdot}C_6H_4Br \begin{cases} C_6H_5{\cdot}N(:O){:}N{\cdot}C_6H_4Br \\ C_6H_5{\cdot}N{:}N(:O){\cdot}C_6H_4Br \end{cases}$$

also confirm the unsymmetrical structure.

[1] S. Goldschmidt and co-workers, *Ber.*, 1920, **53**, 44; 1922, **55**, 616; *Ann.*, 1924, **437**, 194.
[2] H. Wieland, *Ber.*, 1914, **47**, 2111; 1920, **53**, 210; 1922, **55**, 1798. [3] Wallach, *Ber.*, 1880, **13**, 525; 1881, **14**, 2617; Bamberger, *Ber.*, 1900, **33**, 3192. In the above case a small amount of the *o*-compound is also formed. [4] K. von Auwers and Heimke, *Ber.*, 1928, **61**, 1037.

Azo-compounds may be obtained from nitro-compounds by reduction with sodium amalgam or an alkaline solution of stannous chloride, from azoxy-compounds by cautious heating with iron filings, and from hydrazo-compounds by oxidation. As will be seen later, aminoazo-compounds, the amino derivatives of azo-compounds, are formed when hydrochlorides of aromatic amines are warmed with diazoamino-compounds.

The azo compounds are red to yellowish-red crystalline substances, which on further reduction yield first hydrazo-compounds and finally amines. They are very stable and may be distilled without decomposition, differing in this respect from the unstable diazo-compounds to be described later, which contain two nitrogen atoms united with one hydrocarbon radical and an acidic atom or group (*e.g.*, $C_6H_5 \cdot N_2 \cdot Cl$).

Azobenzene, $C_6H_5 \cdot N:N \cdot C_6H_5$, is prepared by distilling azoxybenzene with iron filings:

$$C_6H_5 \cdot N(:O):N \cdot C_6H_5 + Fe = C_6H_5 \cdot N:N \cdot C_6H_5 + FeO$$

It forms orange-red crystals, m.p. 68° and b.p. 295°.

Azobenzene reacts with benzene in the presence of hydrogen chloride and aluminium chloride, giving intermediate products which are convertible into *amino-diphenyl*.[1]

$$C_6H_5 \cdot N:N \cdot C_6H_5 + 2C_6H_6 = 2C_6H_5 \cdot C_6H_4 \cdot NH_2$$

Xylene, diphenyl, naphthalene, anthracene and phenol are still more readily phenylated in this way.

Hydrazo-compounds, $R \cdot NH \cdot NH \cdot R$, are produced by the reduction of azo-compounds with ammonium sulphide, zinc dust and alcoholic potash, sodium amalgam, or sodium amylate. They may also be prepared directly from nitro-compounds by reduction with zinc dust and alkali, or by electrochemical means.

The hydrazo-compounds, which may be regarded as symmetrical derivatives of hydrazine, $NH_2 \cdot NH_2$, are *colourless* neutral substances, which are readily oxidised to azo-compounds. In the presence of mineral acids they undergo a peculiar intramolecular change (see below).

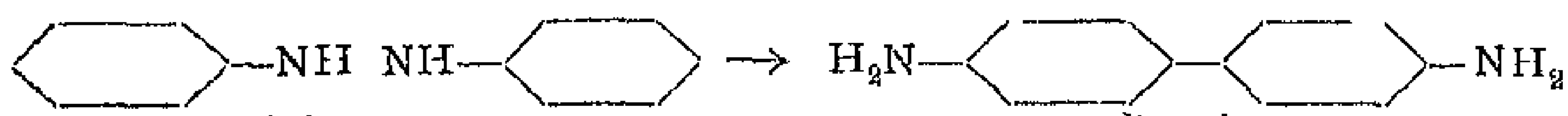
Hydrazobenzene, $C_6H_5 \cdot NH \cdot NH \cdot C_6H_5$, forms colourless leaves or plates, m.p. 131°, is easily oxidised to azobenzene, and with energetic reducing agents yields aniline. When heated, it decomposes into azobenzene and aniline:

$$2C_6H_5 \cdot NH \cdot NH \cdot C_6H_5 = C_6H_5 \cdot N:N \cdot C_6H_5 + 2C_6H_5 \cdot NH_2$$

Under the influence of mineral acids hydrazobenzene undergoes a

[1] R. Pummerer, *Ber.*, 1921, 54, 2768; 1926, 59, 2175.

remarkable intramolecular change, the chief product of the reaction being a base known as *benzidine* or *p*-diamino-diphenyl

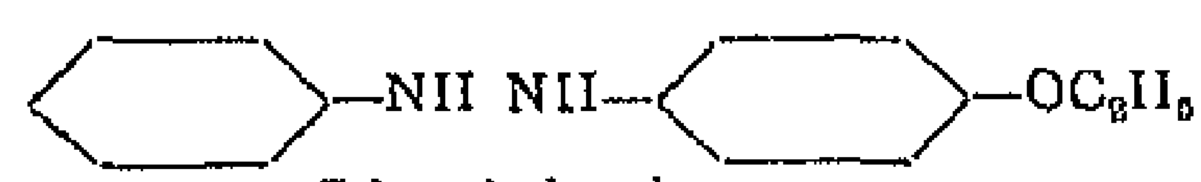


Hydrazobenzene Benzidine

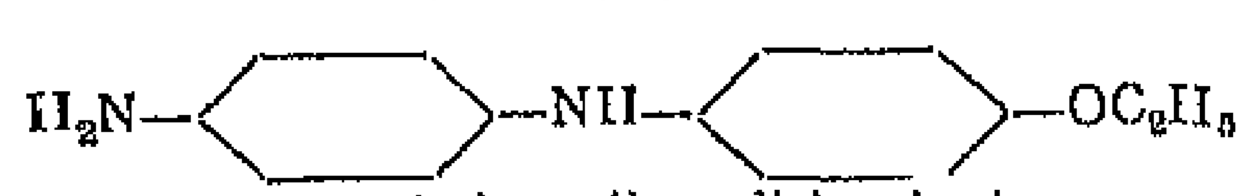
Consequently, when hydrazobenzene is formed by the reduction of azobenzene in acid solution, it is immediately transformed into benzidine. The latter is prepared technically by reducing nitrobenzene to hydrazobenzene by means of zinc dust and sodium hydroxide, and treating the product with acid. Benzidine and its homologue tolidine are of value in the preparation of substantive dyes (see these).

The intramolecular change described above is also undergone by other hydrazo-compounds in which the two para-positions are not substituted, and is known generally as the *benzidine transformation*.

It is obvious that this change cannot take place in the same manner if one of the two para hydrogen atoms of the hydrazo compound is already replaced by a substituent. The course of the reaction in this case was carefully examined by Jacobson and his co-workers,[1] with results which may be summarised as follows. Hydrazo derivatives in which one para position is substituted may undergo a partial transformation to give bases of the type of amino diphenylamine. This process is known as a semi-benzidine or *semidine transformation*, and the resulting products as *semidines*.



p-Ethoxy-hydrazobenzene



p-Amino-*p*-ethoxy-diphenylamine

V.—DIAZO-COMPOUNDS AND HYDRAZINES

The aromatic diazo-compounds containing the group $—N_2—$ are of great importance theoretically as well as practically. They were discovered in 1860 by Griess, as a result of the action of nitrous acid on primary amines of the benzene series. Not only do they afford interesting examples of isomerism, but they are highly reactive and form the starting-point in the preparation of a large number of dye-stuffs. Since diazobenzene hydroxide may play the part of a base, an acid, or an indifferent substance, it is not surprising that chemical opinion as to the constitution of the diazo-compounds passed through many phases[2] prior to the researches of Hantzsch and of Bamberger.

According to Hantzsch, the diazo compounds ArN_2X (where Ar is C_6H_5 or a derivative thereof) may be divided into the following

[1] P. Jacobson, *Ann.*, 1895, 287, 97; 1898, 303, 290. [2] Compare Hantzsch, *Ahrens Sammlung*, VIII, 1902, pp. 1 to 82.

classes, the existence of which is largely dependent on the chemical character of the group X

(*a*) Compounds of the structure $\begin{matrix}Ar.N & X \\ N & \end{matrix}$, such as the *diazonium salts* e.g., $C_6H_5N_2Cl$, which resemble ammonium salts in character

(*b*) Compounds of the structure Ar N N X These are *diazo-compounds* comparable to the azo-derivatives, and sometimes occur in two stereoisomeric forms, viz

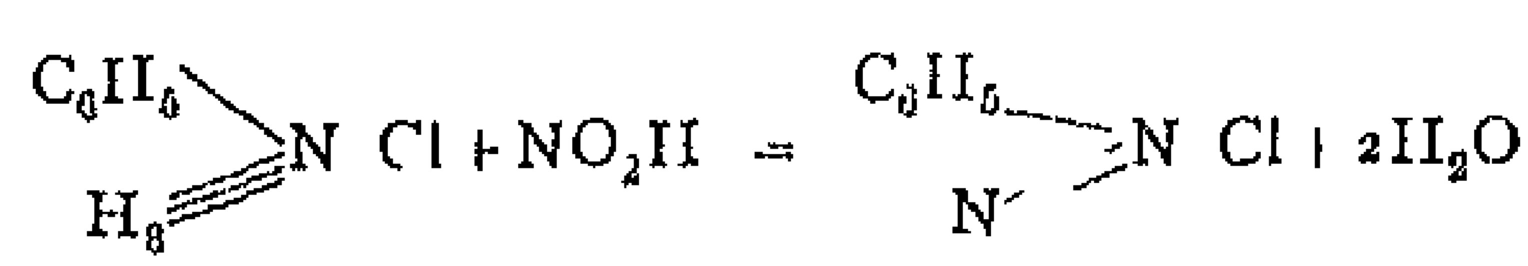
1 *Syn-diazo-compounds* of the type $\begin{matrix}Ar & N \\ X & N\end{matrix}$, which are produced in the first instance, but owing to their extremely labile nature have only been isolated in a few cases

2 *Anti-diazo-compounds* of the structure $\begin{matrix}Ar & N & \\ & N & X\end{matrix}$ These are stable substances

The diazonium salts are by far the most important of the above derivatives, and will therefore be treated in most detail

1 Diazonium Salts

Preparation—If the diazonium salts are only required in solution, their preparation is exceedingly simple A well cooled aqueous solution of a salt of a primary aromatic amine, containing at least one equivalent of free mineral acid, is treated with the calculated amount of sodium nitrite dissolved in water Free nitrous acid is liberated, and *diazotisation* proceeds as in the following equation



Aniline hydrochloride Benzene diazonium chloride

The resulting diazonium salt remains in solution and may be employed directly for the production of other compounds, such as azo-dyes This method of diazotisation is carried out on a very large scale industrially

Owing to the high solubility of most of the diazonium salts in water, and the ease with which they undergo decomposition, a different method has to be adopted for the preparation of the salts in the solid state For this purpose an alcoholic solution of the amine is treated with the requisite acid, and amyl nitrite added to the cooled mixture The salt either separates out immediately or is thrown out by the addition of ether Generally it is even more convenient to diazotise in glacial acetic acid solution [1] It is only in rare instances that the diazonium salt requires to be isolated in the pure state in this manner

[1] Hantzsch and Jochem, *Ber* 1901, 34, 3337

Properties.—Diazonium salts are usually colourless crystalline substances, which are readily soluble in water, less soluble in alcohol, and in the dry state explode violently when heated or struck. In every respect they are genuine salts, comparable to the ammonium and especially to the quaternary ammonium salts. Diazonium nitrates and chlorides are neutral in aqueous solution, and the conductivity figures show them to be ionised to about the same extent as the corresponding potassium and ammonium salts. The resemblance to ammonium salts is also exhibited in the formation and character of complex compounds, such as chloroplatinates, aurochlorides, mercury double salts and diazonium silver cyanides:

$$(ArN_2)_2PtCl_6,\ (ArN_2)AuCl_4,\ (ArN_2)HgCl_3,\ (ArN_2)Ag(CN)_2$$

Diazonium hydrates, $ArN_2 \cdot OH$, have been obtained in solution only, by treating the diazonium chlorides with silver oxide or the sulphates with barium hydroxide. They are very unstable substances, which are proved to be genuine hydroxyl bases[1] by their conductivity and the speed with which they bring about hydrolysis. In this respect their strength varies between that of ammonia and that of the alkali hydroxides.

Reactions of the Diazonium Salts

A number of these reactions, which are used in the preparation of a great variety of benzene derivatives, depend on the ease with which diazonium salts decompose *with elimination of nitrogen*, the place of which is then taken by other atoms or groups.

(1) *Replacement of the N_2-group by hydroxy-, alkoxy-, or acyloxy-groups.* The interaction of diazonium salts with hydroxy-compounds—on warming with water, alcohol, or acetic acid—leads to the formation of phenol or its derivatives as the chief product[2] of reaction, and may be formulated in the case of benzene diazonium chloride in the following manner (intermediate phases being omitted):

$$\underset{\text{Benzene diazonium chloride}}{C_6H_5N_2Cl} + H_2O = \underset{\text{Phenol}}{C_6H_5 \cdot OH} + N_2 + HCl$$

$$C_6H_5N_2Cl + H \cdot OC_2H_5 = \underset{\text{Phenetole}}{C_6H_5 \cdot OC_2H_5} + N_2 + HCl$$

(2) *Replacement of the N_2-group by hydrogen* occurs as a by-reaction in the above decomposition with alcohol.[3] In the case of negatively substituted diazonium salts this becomes the main reaction. Tribromobenzene diazonium salts, for example, yield almost exclusively tribromobenzene, even with very dilute aqueous alcohol:

$$\underset{\text{Tribromobenzene diazonium chloride}}{C_6H_2Br_3 \cdot N_2Cl} + C_2H_5OH = \underset{\text{Tribromobenzene}}{C_6H_3Br_3} + N_2 + HCl + \underset{\text{Acetaldehyde}}{CH_3 \cdot CHO}$$

[1] Hantzsch and Davidson, *Ber.*, 1898, 31, 1612. [2] Hantzsch and Thompson, *Ber.*, 1908, 41, 3519. [3] Hantzsch, *Ber.*, 1901, 34, 3337; 1903, 36, 2061.

Other reducing agents, such as alkaline stannous chloride solution, also replace the nitrogen group by hydrogen

(3) *Replacement of the N_2-group by iodine* occurs on merely warming a solution of a diazonium iodide The reaction is often employed as a preparative method, since many iodo compounds are thus obtained in good yield

$$\underset{\text{Benzene diazonium iodide}}{C_6H_5\cdot N_2\cdot I} = \underset{\text{Iodo-benzene}}{C_6H_5\cdot I} + N_2$$

(4) *Replacement of the N_2-group by chlorine, bromine, or cyanogen* It is not possible to introduce these substituents into the benzene ring in the manner described under (3) above Sandmeyer,[1] however, discovered that the change could be effected with the aid of the corresponding cuprous salts When solutions of the diazonium salts are heated in the presence of cuprous chloride, bromide, or cyanide, there are formed chloro-, bromo-, or cyanobenzenes (*Sandmeyer's reaction*)

$$C_6H_5\cdot N_2\cdot Cl = C_6H_5\cdot Cl + N_2$$
$$C_6H_5\cdot N_2\cdot Br = C_6H_5\cdot Br + N_2$$
$$C_6H_5\cdot N_2\cdot CN = C_6H_5\cdot CN + N_2$$

The Sandmeyer reactions depend in part on the union of the diazo-compound with cuprous salts to form double compounds, which are very easily decomposed

The most important of these reactions is the conversion of diazonium salts into cyano compounds (benzonitriles), from which the corresponding acids are readily obtained by hydrolysis This is a valuable method for the synthesis of aromatic acids

A modification of the above is the *Gattermann reaction*[2] The cuprous salts are here replaced by copper powder, which in the main appears to act catalytically

Diazonium borofluorides decompose on warming to form the corresponding aryl fluoro-compounds,[3] $Ar\cdot N_2\cdot(BF_4) \longrightarrow Ar\cdot F + N_2 + BF_3$

As diazonium salts are readily prepared from nitro-compounds by way of the amines, the reactions just described are frequently employed in the laboratory for converting aromatic nitro compounds into the corresponding hydroxy-, chloro-, bromo-, cyano-, and other derivatives Nitro compounds thus form a valuable means of passing from an aromatic compound to its various derivatives

In addition to these remarkable reactions of the diazonium salts, there are also other important changes which proceed *without elimination of nitrogen*

(1) Diazonium bromides add on bromine to form perbromides, and

[1] Sandmeyer, *Ber*, 1884, 17, 2650, 1687, 20, 1495, 1890, 23, 1630, 1880 [2] *Ber*, 1890, 23, 1218, 1892, 25, 1086 [3] G Balz and G Schiemann, *Ber*, 1927, 60, 1186

these by treatment with ammonia yield diazoimides, which may be regarded as derivatives of hydrazoic acid

$$C_6H_5N_2Br \xrightarrow{+Br_2} C_6H_5N_2Br_3 \xrightarrow{+NH_3} \underset{\text{Benzene diazoimide}}{C_6H_5 \cdot N\Big\langle \begin{matrix} N \\ \| \\ N \end{matrix}} + 3HBr$$

(2) On reduction, diazonium salts are converted into monosubstituted hydrazines (see p 398)

(3) Reactions of the highest importance are those which lead to the production of azo-dyes from diazonium salts, by the "coupling" of the latter with amines and phenols These are dealt with under the heading of azo-dyes (p 400)

2 Diazo Compounds, Ar N NX

When a diazonium salt is treated with alkalis, it is converted into a metallic salt or diazotate of the formula $Ar\ N_2\ OM$, in which the diazohydroxide plays the part of an acid, *e g*

$$C_6H_5\ N_2Cl + 2KOH = \underset{\text{Potassium benzene diazotate}}{C_6H_5\ N\ N\ OK} + KCl + H_2O$$

These diazotates can exist in two isomeric modifications, which are colourless and possess many properties in common Both are readily reduced to hydrazines, and with benzoyl chloride yield nitrosobenzanilides On oxidation both are converted into nitramine salts, *e g* $Ar\ N_2O\ ONa$ They differ mainly in the relative speeds with which they undergo reaction For example, the labile diazotates first formed couple with phenols in alkaline solution to give azo dyes, whereas the stable diazotates obtained by the more prolonged action of alkalis on diazonium salts either fail to give this reaction or react very slowly With mineral acids the diazotates are transformed back into diazonium salts Hantzsch has proved that these diazotates are structurally similar and that their differences are due to stereoisomerism, as illustrated in the following formulæ

$$\underset{\text{Syn diazotate, labile and couples readily}}{\begin{matrix} C_6H_5 & N \\ & \| \\ KO & N \end{matrix}} \qquad \underset{\text{Anti diazotate, stable and couples very slowly or not at all}}{\begin{matrix} C_6H_5 & N & \\ & \| & \\ & N & OK \end{matrix}}$$

According to this view both *syn-* and *anti-diazohydrates* are to be regarded as stereoisomeric oximes of nitrosobenzene Experiment has shown that both forms are actually produced by the interaction of hydroxylamine and nitrosobenzene

$$Ar\ N\ O + H_2N\ OH \xrightarrow{KOH} Ar\ N\ N\ OK + H_2O$$

In this reaction labile syn-forms are first obtained, which then pass into the stable anti-modifications.[1]

Stereoisomerism of a similar type has also been found to exist in the case of the diazo-sulphonates, Ar.N:N.SO_3K, and the diazo-cyanides, Ar.N:N.CN. These are obtained from diazonium salts by the action of potassium sulphite and potassium cyanide respectively:

$$\underset{\text{Diazonium salt}}{Ar.N_2X} + K.SO_3K = \underset{\text{Diazo-sulphonate}}{ArN_2.SO_3K} + KX$$

$$Ar.N_2X + KCN = \underset{\text{Diazo-cyanide}}{Ar.N_2.CN} + KX$$

Relationship between Nitrosamines and Diazo-Compounds

Primary Nitrosamines and Anti-diazohydrates.—The group —N_2OH in the compounds R.N_2OH is tautomeric, functioning either as an anti-diazohydrate (-N:N.OH) or as a primary nitrosamine structure (.NH.NO). According to the researches of Hantzsch and his co-workers,[2] all the metallic salts, R.N_2OM, are to be regarded as anti-diazotates, but the free hydrogen derivatives may exist either as diazohydrates, R.N:N.OH, or, as more frequently happens, as primary nitrosamines, R.NH.NO. Hence, in the latter case, during the conversion of the salt (diazotate) into the hydrogen compound, an intramolecular rearrangement takes place, Ar.N:N.OK ⟶ Ar.NH.NO. Conversely, the primary phenyl nitrosamines behave as pseudo-acids, reacting with alkalis to form salts of the anti-diazohydrate structure. The anti-diazotates are thus closely related to the nitrosamines.

The isolation of both isomeric forms of the hydrogen compound from one and the same tautomeric substance has been effected in a few instances, *e.g.*, in the case of 2:4:6-tribromobenzene anti-diazohydrate, $C_6H_2Br_3$.N:N.OH, and the corresponding nitrosamine,[3] $C_6H_2Br_3$.NH.NO. These isomerides recall the somewhat similar aliphatic nitroso-compounds, R_2CH.NO and R_2C:N.OH, and their formation is analogous to that of the isomeric nitro-compounds (pp. 154 and 156). In chemical behaviour the isomerides differ in accordance with the formulæ given above. The anti-diazohydrates resemble reactive hydroxy-acids, whereas the nitrosamines are indifferent pseudo-acids.

Secondary Nitrosamines and Anti-diazotates.—The alkylation of an anti-diazotate, ArN:NOK, results generally in the formation of a nitrosamine of a secondary base, Ar.NAlk.NO. Conversely, certain nitroso-alkylanilines are readily converted into anti-diazotates by treatment with dilute alkalis. Hence the nitroso-derivatives of secondary aromatic amines are also intimately related to the anti-diazo-compounds.

$$\underset{\substack{\text{Secondary}\\ \text{nitrosamine}}}{C_6H_5.N\begin{cases}NO\\ Alk\end{cases}} \;\underset{\text{Alkylation}}{\overset{\text{KOH}}{\rightleftarrows}}\; \underset{\text{Anti-diazotate}}{C_6H_5.N:N.OK}$$

Phenyltriazene (benzene diazoamide),[4] C_6H_5.N:N.NH_2, has been obtained by the reduction of diazobenzene imide in ethereal solution with stannous chloride. It crystallises in colourless leaflets, which melt with evolution of gas at 50°, and readily decompose into aniline and nitrogen: $C_6H_5.N_3H_2 = C_6H_5.NH_2 + N_2$. It reacts, on

[1] Hantzsch, *Ber.*, 1905, 38, 2056. [2] *Ber.*, 1899, 32, 1703; 1900, 33, 2188. [3] Hantzsch and Pohl, *Ber.*, 1902, 35, 2964. [4] O. Dimroth, *Ber.*, 1907, 40, 2376.

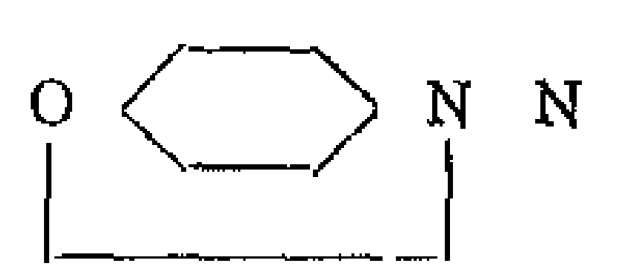
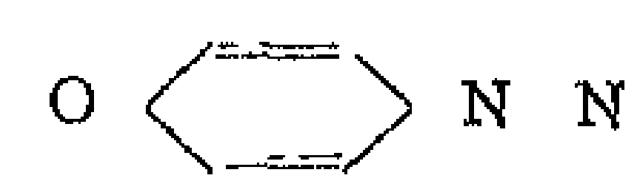
the one hand, according to formula I, and on the other as a phenyl cyclo triazane II, and therefore appears to be a tautomeric compound

$$\text{I}\quad C_6H_5\,N{:}N{\cdot}NH_2 \qquad\qquad \text{II}\quad C_6H_5\,N\!<\!\begin{matrix}NH\\ |\\ NH\end{matrix}$$

Diazohydrates, Diazoanhydrides and Quinone-diazides
Sensitiveness of Diazo Compounds towards Light

When diazonium chloride solutions are treated with a small excess of silver oxide there are obtained solutions of the very unstable diazonium hydroxides, *e g* $C_6H_5N_2OH$ The normal (*syn*-) metallic diazotates on careful addition of acetic acid do not yield the hydrates, but deposit the corresponding *diazoanhydrides*[1] (*diazo oxides*)

Hydroxyphenyl diazonium salts, containing the OH group in the *o*- or *p*-position, on treatment with alkalis form internal anhydrides of the diazonium type (I) or of the quinone type (II)

I  II 

Hence they are described as quinone-diazides[2]

Owing to their sensitiveness to light, diazo compounds are now being used in the manufacture of photographic tracing paper[3] In the earlier process the paper, film, etc, was sensitised with diazoanhydrides and after exposure to light was developed by coupling with phenols or amines The irradiated anhydride is non reactive and a positive original thus gives rise to a positive azo dyestuff copy The paper is very sensitive and retains its activity a long time In a later modification the diazo and azo dyestuff components are coated together on the paper with the addition of tartaric acid, which prevents coupling After exposure the paper is developed with dry gaseous ammonia A suitable diazo compound is, for example, diazotised 1 2 4 aminonaphthol sulphonic acid, resorcinol being employed as azo component The process is known as diazotype printing

Hydrazines

Aromatic hydrazines are classified in the same manner as the aliphatic compounds (see p 164) Symmetrical disubstituted aromatic hydrazines, usually termed hydrazo-compounds, have already been dealt with on p 391

The *monosubstituted hydrazines*, of which phenyl-hydrazine, $C_6H_5\,NH\,NH_2$, is the best known example, are the most important

[1] E Bamberger, *Ber*, 1896, 29, 459 [2] L. Wolff, *Ann*, 1900, 312, 126 H Staudinger, *Helv Chim Acta*, 1922, 5, 87 [3] Kogel, D R.P, 376385, 386433 See also Ruff and Stein, *Ber*, 1901 34, 1668 D A Spencer, *Photographic Journal*, 1928, 68, 490 Ozalidpaper, and Ozaphanfilm (Kalle & Co, Germany) are prepared by this process

These are generally prepared by the reduction of the corresponding diazonium salts, which may be effected in two ways —

(*a*) By treating diazonium salts with the calculated amount of stannous chloride in hydrochloric acid solution

$$C_6H_5 \cdot N_2 \cdot Cl + 4H = \underset{\text{Phenyl hydrazine hydrochloride}}{C_6H_5NH \cdot NH_2, HCl}$$

(*b*) According to the older method of Emil Fischer, by which phenyl-hydrazine was first discovered. The solution of a diazonium salt is allowed to react with neutral sodium sulphite, whereby a diazo-sulphonate (see p. 397) is formed, *e.g.*

$$C_6H_5 \cdot N_2 \cdot Cl + Na_2SO_3 = \underset{\text{Sodium diazobenzene sulphonate}}{C_6H_5 \cdot N:N \cdot SO_3Na} + NaCl$$

On reduction with sulphurous acid, or zinc dust and acetic acid, the diazo-sulphonate is converted into a hydrazine-sulphonate,

$$C_6H_5N:NSO_3Na + 2H = \underset{\text{Sodium phenyl hydrazine sulphonate}}{C_6H_5 \cdot NH \cdot NH \cdot SO_3Na}$$

When this is heated with hydrochloric acid, the sulphonic group is removed and phenyl-hydrazine hydrochloride obtained.

$$C_6H_5 \cdot NH \cdot NH \cdot SO_3Na + H_2O + HCl = C_6H_5 \cdot NH \cdot NH_2, HCl + NaHSO_4$$

In each of the above methods an amine forms the starting-point, and it is converted into the diazonium salt, and finally into the hydrazine, without actually isolating any of the intermediate products.

The monosubstituted hydrazines are monacid bases, which distil without decomposition under diminished pressure. They are sparingly soluble in water, readily soluble in alcohol and ether, and reduce Fehling's solution.

Phenyl hydrazine, $C_6H_5 \cdot NH \cdot NH_2$, is prepared on the large scale according to method (*b*) described above. It is a colourless liquid which boils with slight decomposition at 241°, under atmospheric pressure. On cooling it solidifies to large colourless prisms, m.p. 19.6°. The hydrochloride crystallises in white leaflets, which are not very soluble in cold water, and dissolve very sparingly in concentrated hydrochloric acid.

As has already been mentioned, phenyl-hydrazine is a valuable reagent for aldehydes and ketones, and has proved of special service in the investigation of the sugars (see p. 290 *et seq.*). It is a strong reducing agent, and precipitates cuprous oxide from Fehling's solution,

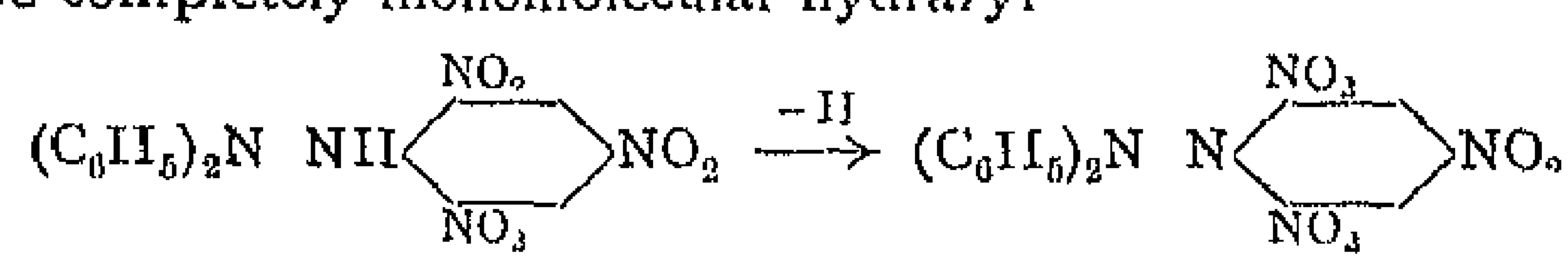
in such reactions the phenyl-hydrazine decomposes into benzene, nitrogen and hydrogen

$$C_6H_5 \cdot NH \cdot NH_2 = C_6H_6 + N_2 + 2H$$

When treated with energetic reducing agents it yields aniline and ammonia, $C_6H_5 \cdot NH \cdot NH_2 + 2H = C_6H_5 \cdot NH_2 + NH_3$. Phenyl-hydrazine unites with β-diketones and β-ketonic esters to form derivatives of pyrazole and pyrazolone respectively. Acetoacetic ester, for example, gives phenyl-methyl-pyrazolone, which on methylation is converted into antipyrine, a substance extensively used in medicine as a febrifuge. Owing to its use in the preparation of *antipyrine*, phenyl-hydrazine is produced in large quantities industrially.

The behaviour of *tetraphenyl hydrazine* in dissociating in solution into *nitrogen diphenyl* has already been discussed on p. 389. Hexaphenyl ethane decomposes in a similar manner to form triphenyl methyl (p. 509).

Reference has also been made to the dissociation of *hexaphenyl-tetrazane* into two molecules of *triphenyl-hydrazyl*. In the solid state hexaphenyl-tetrazane is colourless; in solution at 0° it is deep blue, although the blue triphenyl-hydrazyl is extremely unstable. A more stable divalent nitrogen derivative may be obtained from *αα-diphenyl-β-trinitrophenyl hydrazine*, a yellowish red crystalline substance, which when oxidised in benzene or chloroform solution with lead dioxide yields the monomolecular *αα-diphenyl-β trinitrophenyl hydrazyl*. The latter forms violet black crystals, soluble in organic solvents to give deep violet solutions. In the above reaction the hydrazine is converted into the completely monomolecular hydrazyl.



This compound is the analogue of tribiphenylmethyl (described later) and is distinguished from other derivatives of divalent nitrogen by its great stability.[1]

VI.—AZO-DYES

General Methods of Formation

It has already been remarked (see p. 396) that diazo-compounds "couple" with amines and phenols with great readiness to form azo-dyes. Although this process has been formulated in the following pages as a simple change, it is in all probability one of some complexity.[2]

(*a*) Equimolecular quantities of diazonium salts and *primary* or

[1] S. Goldschmidt and Renn, *Ber.*, 1922, **55**, 628. [2] See Chattaway and H. R. Hill, *J. C. S.*, 1922, **121**, 2756.

secondary aromatic amines react together to form *diazoamino-compounds*,[1] e.g.

$$C_6H_5N_2Cl + H_2N\cdot C_6H_5 = \underset{\text{Diazoaminobenzene}}{C_6H_5\cdot N:N\cdot NHC_6H_5} + HCl$$

The most interesting property of these compounds is their transformation into the structurally isomeric **aminoazo-compounds**. In the case of diazoaminobenzene this change can be effected by merely allowing the substance to stand in alcoholic solution, and may be catalytically accelerated by the addition of a small amount of aniline hydrochloride.[2]

Diazoaminobenzene → Aminoazobenzene

The isomerisation only takes place readily when the *p*-position to the amino group is free. If this is already occupied by a substituent the change occurs less easily, and the amino-group then enters the *o*-position to the azo group. Diazoamino-*p*-toluene, for example, yields *o*-aminoazotoluene.

Aminoazobenzene is the parent substance of a large number of azo-dyes.

(*b*) Diazonium salts and *tertiary* aromatic amines react directly with one another to form aminoazo-compounds:

$$C_6H_5\cdot N_2\cdot Cl + HC_6H_4\cdot N(CH_3)_2 = \underset{\text{Dimethylaminoazobenzene}}{C_6H_5\cdot N:N\cdot C_6H_4\cdot N(CH_3)_2} + HCl$$

(*c*) In a similar manner phenols unite with diazonium salts in the presence of alkalis, to form hydroxyazo compounds:

$$C_6H_5\cdot N_2\cdot Cl + \underset{\text{Phenol}}{HC_6H_4(OH)} = \underset{\text{Hydroxyazobenzene}}{C_6H_5\cdot N:N\cdot C_6H_4\cdot OH} + HCl$$

Here also it has been found that only those hydrogen atoms in the *o*- or *p*-positions to the phenolic hydroxy-group are capable of entering into reaction. If hydrogen is only available in the *m*-position, no

[1] Diazoamino compounds are also formed by the action of organomagnesium halides on alkyl and aryl derivatives of hydrazoic acid. Intermediate products containing magnesium are

$$\text{I.}\quad R\cdot N\langle{N \atop N}\rangle + R'MgI = R\cdot N(MgI)\cdot N:N\cdot R'$$

$$\text{II.}\quad R\cdot N(MgI)\cdot N:N\cdot R' + H_2O = R\cdot NH\cdot N:N\cdot R' + MgI\cdot OH$$

first formed, which on treatment with water yield diazoamino compounds. O. Dimroth, *Ber.*, 1905, 38, 670. [2] Goldschmidt has shown that the velocity with which diazoamino compounds are transformed into aminoazo compounds, $Ar\cdot N:N\cdot NHC_6H_5, HX \longrightarrow Ar\cdot N:N\cdot C_6H_4\cdot NH_2, HX$, is proportional to the degree of dissociation of the acid HX in the solvent employed.

coupling takes place unless the substituents in the reactive positions are particularly easily detached.[1]

The instances already quoted are simple examples of the typical reactions by which the great majority of the monoazo-dyes are prepared. It is readily understood that these reactions are influenced by the specific constitution of both reagents, and that the velocity of coupling depends on the structure of the amines and phenols, as well as on that of the diazo-compound employed. The introduction of alkyl groups into the benzene ring increases this velocity, but halogen atoms have the reverse effect; thus the trimethyl derivatives, $(CH_3)_3C_6H_2\cdot N_2X$, react very rapidly, and the tribromo-compounds, $Br_3C_6H_2\cdot N_2X$, very slowly. The great influence exerted by the configuration of the diazo group has already been emphasised (p. 396), the speed of reaction of syndiazo-compounds being always greater than that of the anti-compounds. This fact is of great value in determining the structure of stereoisomerides of this type. Finally, it may be mentioned that the formation of aminoazo compounds from diazonium salts and salts of tertiary amines is retarded by acids and bases alike,[2] the velocity of reaction being inversely proportional to the concentration of hydrogen ions or hydroxyl ions respectively.

Disruption of Azo-dyes

A point of great importance in connection with the structure of the azo-dyes is the behaviour of these compounds towards powerful reducing agents, such as tin and hydrochloric acid. Under this treatment the molecule is disrupted at the double bond —N=N—, so that the amine from which the azo-dye was prepared by diazotisation is regenerated, and the second component with which the diazonium salt was originally coupled is obtained in the form of its amino derivative. For example, hydroxy-azobenzene, from diazotised aniline and phenol, yields aniline and *p*-aminophenol on reduction:

$$\underset{\text{Hydroxy-azobenzene}}{C_6H_5\cdot N:N\cdot C_6H_4\cdot OH} + 4H = \underset{\text{Aniline}}{C_6H_5\cdot NH_2} + \underset{p\text{-Aminophenol}}{H_2N\cdot C_6H_4\cdot OH}$$

Hence it may be deduced that in the formation of the azo-dye the coupling occurred in the *p*-position to the phenolic —OH group.

The azo-dye may also be decomposed by treatment with strong nitric acid, which leads in general to the production of the original diazonium salt and a nitro-derivative of the original coupling component,[3] *e.g.*:

$$\underset{p'\text{-Nitro-}p'\text{-methoxy-azobenzene}}{O_2N\cdot C_6H_4\cdot N:N\cdot C_6H_4\cdot OCH_3} + 3HNO_3$$

$$= \underset{p\text{-Nitrobenzene diazonium nitrate}}{O_2N\cdot C_6H_4\cdot N_2\cdot NO_3} + \underset{2:4\text{-Dinitro-anisole}}{(O_2N)_2\cdot C_6H_3\cdot OCH_3} + 2H_2O$$

[1] Even the *o*- and *p*-hydrogen atoms cannot always be replaced by azo groups, *cf.* Borsche and Streitberger, *Ber.*, 1904, 37, 4116. [2] H. Goldschmidt, *Ber.*, 1899, 32, 355. [3] O. Schmidt, *Ber.*, 1905, 38, 3201.

Azo-compounds as Dyes; Technical Preparation and Description of Individual Dyes

The divalent azo-group —N N— is the *chromophore* of the azo-dyes When this group is introduced into a hydrocarbon molecule, a coloured substance is obtained which is not a dye Only after the further entry of an *auxochrome* group, such as —OH or —NH_2, capable of conferring acidic or basic character on the compound, does it acquire the property of affixing itself to threads and fibres and thus of functioning as a dye (see p 74)

The simplest azo-dyes, like those of other types, dye a yellow colour By increasing the number of auxochrome groups present, or by raising the proportion of carbon in the molecule, the shade gradually deepens, passing through red to violet and blue, or in some cases to brown In particular, the introduction of naphthalene residues changes the colour to red, violet, blue, and finally to black Those aminoazo- and hydroxy-azo-compounds in which no sulphonic group is present, are generally insoluble or only sparingly soluble in water To be useful, however, a dye must be soluble in water, and since the alkali salts of the sulphonic acid derivatives are more readily soluble than the unsulphonated parent dye-stuffs, the compounds employed technically are for the most part sulphonic derivatives Azo dyes are therefore usually prepared directly from sulphonic acids, or the dye may be subsequently sulphonated by treatment with strong sulphuric acid

Monoazo-dyes directly colour threads of animal origin, such as wool and silk, whereas they only dye cotton indirectly, with the aid of mordants

Dyeing[1]

The dyeing of spun threads may be mechanical or chemical In the former case, which does not further concern us, a coloured precipitate (pigment) is produced on the threads, or the latter are coated with a thin layer of a coloured substance Of much greater interest is chemical dyeing, in which the fabric is usually immersed in a hot aqueous solution of the dye, removing the latter from the solution and becoming thereby coloured No satisfactory explanation can at present be advanced which will cover all the different processes of chemical dyeing The majority of chemists assume that in many cases, at all events, dyeing is dependent on a kind of salt formation between the dye and the constituents of the thread, an assumption supported by the fact that a dye always possesses basic or acidic character

[1] See *The Synthetic Dyestuffs*, by J C Cain and J F Thorpe, (Griffin); *Dye Chemistry*, by Fierz David (Churchill, English edition by F A Mason); *Synthetic Colouring Matters, Vat Colours*, J F Thorpe and C K Ingold (Longmans, 1923)

Probably the dye is bound to the fibre by the amino-, carboxyl and acid amide groups present in the surface of the threads. It must be emphasised that a characteristic difference is shown between yarns of animal (wool, silk) and those of vegetable origin (cotton, artificial silk). Most dyes colour the former directly (*substantive* or *direct dyeing*) but are not capable of dyeing vegetable threads without special treatment. It is, however, possible to fix the colour to the latter if the fabric is previously impregnated with certain substances which will unite with the dye (*adjective dyeing*). Substances of this type are termed *mordants*. In working with basic dyes, mordants such as tannin are employed, which combine with the dye to form insoluble salts, *e.g.* of tannic acid. In most cases the process is completed by treatment with a solution of potassium antimonyl tartrate. With acid dye-stuffs, on the other hand, cotton requires to be impregnated with a basic mordant such as aluminium, iron or chromium hydroxides. The fabric is steeped in an aqueous solution of the metallic acetate and then heated in steam, whereby the acetate is decomposed with the production of the corresponding hydroxide. Acid dyes combine with these hydroxides to form insoluble "lakes". As will be seen later, alizarin dyes are commonly employed in this manner. Dye-stuffs are also known which are capable of colouring cotton directly or substantively, *i.e.* without the addition of mordants, in the same way as the wool dyes affix themselves to wool. Chief among this class are azo-dyes obtained from benzidine, $NH_2 . C_6H_4 . C_6H_4 . NH_2$, and its derivatives, which contain two of the chromophore groups —N : N—. These are distinguished from monoazo-dyes by the term *disazo-* or *tetrazo-dyes*.

The technical preparation of azo-dyes is generally a comparatively simple operation. In order to obtain hydroxyazo-dyes by the combination of diazo-compounds with phenols, a solution of a diazonium salt is first prepared by treating an aqueous solution or suspension of the required amine, or its sulphonic acid salt, with the requisite amounts of hydrochloric acid and sodium nitrite. After diazotisation is completed, the liquid is allowed to run into an alkaline solution of the desired phenol, or better still, of its sulphonic acid salt, care being taken that the mixture remains alkaline throughout the reaction. The resulting azo-dye is thrown out of solution by the addition of common salt, filtered in a filter press, and dried. Combination between diazonium salts and amines, which leads to the formation of aminoazo-dyes, is effected directly in neutral aqueous solution, or in many cases by adding an alcoholic solution of the amine to a concentrated aqueous solution of the diazo compound.

A detailed description of the azo dyes is not possible in a general text book such as this. The following examples are selected from the very large and ever-increasing number of these compounds known, of which only those of good colour and fastness to light are used in industry.

Dimethylamino azobenzene sulphonic acid,[1] $\overset{1}{SO_2}\cdot C_6H_4\cdot\overset{4}{NH}\cdot\overset{1}{N}=C_6H_4=\overset{4}{\overset{O}{N}}(CH_3)_2$, is produced by the action of dimethylaniline on a diazotised solution of sodium sulphanilate The sodium salt of the compound dyes wool and silk an orange colour, and has been employed for this purpose under the name of **helianthine** or **methyl orange** It is largely used as an indicator in volumetric analysis, the yellow colour of the aqueous solution changing to red on acidification

Chrysoidine, *diamino azobenzene*,

$$C_6H_5\cdot N:\overset{4}{N}\cdot C_6H_3\begin{cases}\overset{1}{N}H_2\\ \underset{3}{N}H_2\end{cases}$$

is prepared by mixing equivalent solutions of benzene diazonium chloride and *m* phenylene diamine Its hydrochloride is comparatively soluble in water and is used in dyeing wool, particularly for pale shades Wool mordanted with tannin is coloured orange yellow

Bismarck brown, *triamino azobenzene*, $H_2N\cdot C_6H_4\cdot N:N\cdot C_6H_3(NH_2)_2$, is formed by the action of nitrous acid on *m* phenylene diamine It resembles chrysoidine in its properties, and is employed for dyeing wool and leather goods

Tropaeoline O, *dihydroxy azobenzene*-p *sulphonic acid*,

$$\overset{1}{SO_3H}\cdot C_6H_4\cdot\overset{4}{N}:\overset{1}{N}\cdot C_6H_3\begin{cases}\overset{2}{O}H\\ \underset{4}{O}H\end{cases}$$

is obtained by pouring a diazotised solution of sulphanilic acid into an alkaline solution of resorcinol, or by coupling benzene diazonium chloride with resorcinol and subsequently treating the product with sulphuric acid In acid solution it colours wool and silk golden yellow, and is used more particularly in the silk industry

Among the substantive azo dyes, which, as already mentioned, are able to dye cotton directly without the aid of mordants, are included certain compounds obtained by diazotising *p* diamines and combining the bis diazonium salts thus formed with amines and phenols, particularly with naphthols and naphthol sulphonic acids For example, when benzidine is diazotised and coupled with α naphthionic acid, it yields **Congo red**, which is much used in dyeing

$$\begin{array}{l} C_6H_4-N{=}N-C_{10}H_5\begin{cases}SO_3H\\ NH_2\end{cases}\\ |\\ C_6H_4-N{=}N-C_{10}H_5\begin{cases}SO_3H\\ NH_2\end{cases}\end{array}$$

Congo red

VI

Aromatic Sulphonic Acids

Formation—When aromatic hydrocarbons or their derivatives are treated with sulphuric acid they yield sulphonic acids, in which hydrogen of the benzene nucleus is replaced by the sulphonic group SO_3H, *eg* $C_6H_6+H_2SO_4 = C_6H_5\cdot SO_3H+H_2O$ *Sulphonation* is

[1] The numbers attached to this and the following formulæ indicate the position of the substituents in the benzene nucleus In the above case the free acid possesses a quinonoid structure Hantzsch, *Ber.*, 1908, **41**, 2435 Fox, *Ber*, 1908, **41**, 1989

effected by the use of ordinary sulphuric acid,[1] or of fuming acid containing varying proportions of anhydride, the temperature being regulated according to the ease with which the reaction occurs In this way, by choosing the conditions, it is possible to prepare mono- or polysulphonic acids In the case of benzene a maximum of three sulphonic groups may thus be introduced into the molecule[2] The sulphonic acids either separate directly from the acid mixture on cooling, or are precipitated in the form of their alkali salts by the addition of salt, sodium acetate or potassium chloride They may also be separated from the excess of sulphuric acid as the soluble calcium, barium or lead salts

Properties and Chemical Behaviour —The sulphonic derivatives of the hydrocarbons are all readily soluble in water, and form more or less easily crystallisable substances of strongly acidic character By the action of superheated steam, or of concentrated hydrochloric acid at 150°, they may be converted into the original hydrocarbon (see p 370) When fused with alkalis they yield phenols, a reaction which is of great importance technically

$$C_6H_5 \cdot SO_3K + KOH = C_6H_5 \cdot OH + K_2SO_3$$

On being heated with potassium cyanide the salts of sulphonic acids pass into the corresponding nitriles, which may be hydrolysed to carboxylic acids

$$\underset{\text{Potassium benzene sulphonate}}{C_6H_5 \cdot SO_3K} \xrightarrow{KCN} \underset{\text{Benzonitrile}}{C_6H_5 \cdot CN} \longrightarrow \underset{\text{Benzoic acid}}{C_6H_5 \cdot COOH}$$

The alkali salts of the sulphonic acids, on being treated with phosphorus pentachloride, yield *sulphonic chlorides* of the formula $R \cdot SO_2 \cdot Cl$ With ammonia or ammonium carbonate, these give crystalline *sulphonamides*, $R \cdot SO_2 \cdot NH_2$ The latter are frequently used in the identification of the sulphonic acids The *anhydrides* are colourless neutral substances, which generally crystallise well and are remarkably stable towards water or weak alkalis[3]

Benzene sulphonic acid, $C_6H_5 \cdot SO_3H$, crystallises in plates, m p 66°, which very readily dissolve in water Its chloride may be used for distinguishing between primary and secondary amines (p 162) — **Benzene disulphonic acids**, $C_6H_4(SO_3H)_2$ When benzene is heated with fuming sulphuric acid, a mixture of the *m* disulphonic acid, m p 63°, with a little *p* compound, m p 132°, is formed The sulphonation of toluene leads mainly to the formation of **o and p toluene sulphonic acids**

The nitration of benzene sulphonic acid or the sulphonation of nitrobenzene yields in each case a mixture of *o-, m and p-nitrobenzene sulphonic acids*, containing a preponderance of the *m* compound On reduction these yield the three *aminosulphonic acids*, which are colourless crystalline compounds having acidic, but no basic, properties The

[1] A Guyot, *C*, 1920, I, 565 [2] R Behrend and Mertelsmann, *Ann*, 1911, 378, 352.
[3] H Meyer and Schlegel, *Monats*, 1913, 34, 561

sulphonic acids derived from primary amines may be diazotised and are of value in the preparation of azo-dyes (p 404)

Sulphanilic acid, p-*aminobenzene sulphonic acid*,

$$C_6H_4\left\langle\begin{matrix}NH_2\\ SO_2OH\end{matrix}\right. \qquad \text{or} \qquad C_6H_4\left\langle\begin{matrix}NH_3\\ SO_2\end{matrix}\right\rangle O$$

is obtained by heating aniline to 180° with fuming sulphuric acid containing 8 to 10 per cent of anhydride It is only sparingly soluble in cold water, and crystallises in rhombic plates ($+2H_2O$) It yields quinone on oxidation with chromic acid, and is an important starting material in the preparation of azo-dyes

Metanilic acid, or m-*aminobenzene sulphonic acid*, is also used in the manufacture of dyes and is obtained from *m*-nitrobenzene sulphonic acid by reduction with iron and hydrochloric acid

Phenol sulphonic acids, sulphobenzoic acids, and other more complex sulphonic derivatives are dealt with in later chapters

Sulphinic acids, $R\ SO_2H$, may be prepared by reducing arylsulphonic chlorides with zinc dust and water They are crystalline

$$C_6H_5.SO_2Cl \longrightarrow C_6H_5\ SO_2H$$

compounds which dissolve sparingly in cold water

VII

Aromatic Arsenic Compounds[1]

Mainly in consequence of the researches of P Ehrlich, organic compounds of arsenic have, in the last twenty years, been extensively employed in medicine Only a few of the more important of these will be treated here

Primary Aromatic Arsonic (Arsinic) Acids

Preparation—It was shown by Ehrlich and Bertheim that the arsenic compound discovered in 1863 by Béchamps, by heating aniline arsenate, and employed in medicine under the name of *atoxyl*, was not, as Béchamps assumed, an anilide of arsenic acid, but *p*-aminophenylarsonic acid

In general, when primary aromatic amines are fused with arsenic

[1] See *Organic Compounds of Arsenic and Antimony*, by G T Morgan (Longmans, Green & Co, 1918) *Organische Arsenverbindungen und ihre chemotherapeutische Bedeutung*, by Nierenstein (Enke, Stuttgart, 1912) *Handbuch der organischen Arsenverbindungen*, by A Bertheim (Enke, 1913) L. F Hewitt, H King and W O Murch, *J C S*, 1926, 1355

acid, the arsenic group takes up the para-position with respect to nitrogen, with the formation of *p*-aminoaryl arsonic acids If the *p* position is already occupied, then either no substitution occurs or the corresponding *o* amino-derivative is obtained

$$NH_2 \cdot C_6H_5 + AsO_4H_3 = NH_2 \cdot C_6H_4 \cdot AsO_3H_2 + H_2O$$

Many other aromatic compounds, such as phenols and certain indoles, behave in the same manner

This process is an exact parallel to the production of sulphanilic acid by the action of heat on aniline sulphate (p 407), and may therefore be described as *arsenation* (*cf* sulphonation) and the reaction products as *arsanilic acids* Most of the aminoaryl arsonic acids known have been prepared in this way

Among other syntheses of aromatic arsenic derivatives the following may be mentioned On treating diazo-compounds with arsenious acid or its salts the diazo group is replaced by arsenic to give primary arsonic acids[1]

$$RN:NX + As(OH)_3 = R \cdot AsO(OH)_2 + N_2 + HX$$

This reaction may also be used to prepare the corresponding antimony derivatives Acids containing both these metals are obtained by the interaction of antimony oxide with diazotised aminophenylarsonic acids (or of arsenites with diazotised aminophenylantimonic acids), in this manner phenylene-arsonic-antimonic acids are formed[2] ($C_6H_4 \cdot AsO_2 \cdot SbO_2 \cdot nH_2O$)

Properties—Aromatic amino-arsonic acids are very reactive and may be used in a variety of syntheses In particular they are readily diazotised, and the diazoaryl arsonic acids so obtained undergo the usual decompositions of diazo compounds (see p 394), and couple in the usual manner to give azo-dyes, all of which are soluble in alkalis owing to the presence of the arsenic acid residue, AsO_3H_2 In its properties this group shows a general resemblance to the sulphonic group, SO_3H, and in some reactions to the carboxyl group, CO_2H

_p_-Aminophenylarsonic acid, Arsanilic acid, $H_2N \cdot C_6H_4 \cdot AsO_3H_2$, is the most important of these acids, and, as already described, is obtained by the arsenation of aniline It crystallises in colourless needles, and is difficultly soluble in cold water, in hot water it dissolves easily to give an acid solution As an acid the compound is readily soluble in alkalis, but it also possesses basic properties, as shown by its solubility in an excess of dilute mineral acid It does not melt at any particular temperature, but decomposes in the neighbourhood of 300° The sodium salt has been employed in medicine under the

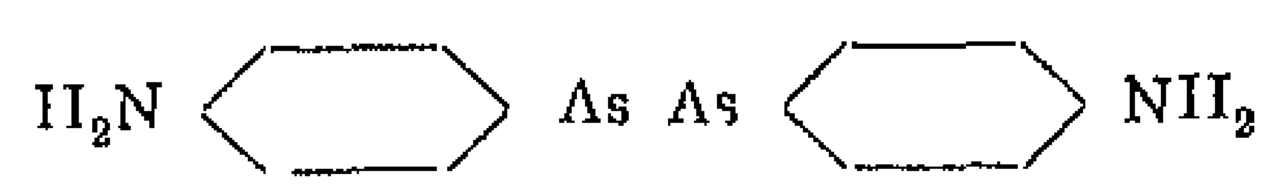
[1] H Bart, D R P 250264 *Ann*, 1922, 420, 55 P Sakellarios, *Ber*, 1924, 57, 1514 E Maschmann, *Ber*, 1924, 57, 1759 [2] Hans Schmidt, *Ber*, 1924, 57, 1124

name of *atoxyl* in cases of syphilis and sleeping sickness In the year 1902, when this substance was first placed on the market, experiments were being carried out by Ehrlich and Shiga with the object of curing parasitic diseases by the injection of suitable chemical compounds In this work the action of atoxyl on trypanosomes was investigated, with results which led to further experiments with arsenic derivatives and to the valuable discovery of salvarsan

Reduction Products of Arsanilic Acids

pp'-*Diamino-arsenobenzene*[1]

On energetic reduction the arylarsonic acids are converted into arseno-compounds, that produced from *p*-aminophenyl arsonic acid (arsanilic acid) being *pp'*-diamino-arsenobenzene or *p*-arsenoaniline, possessing the structure



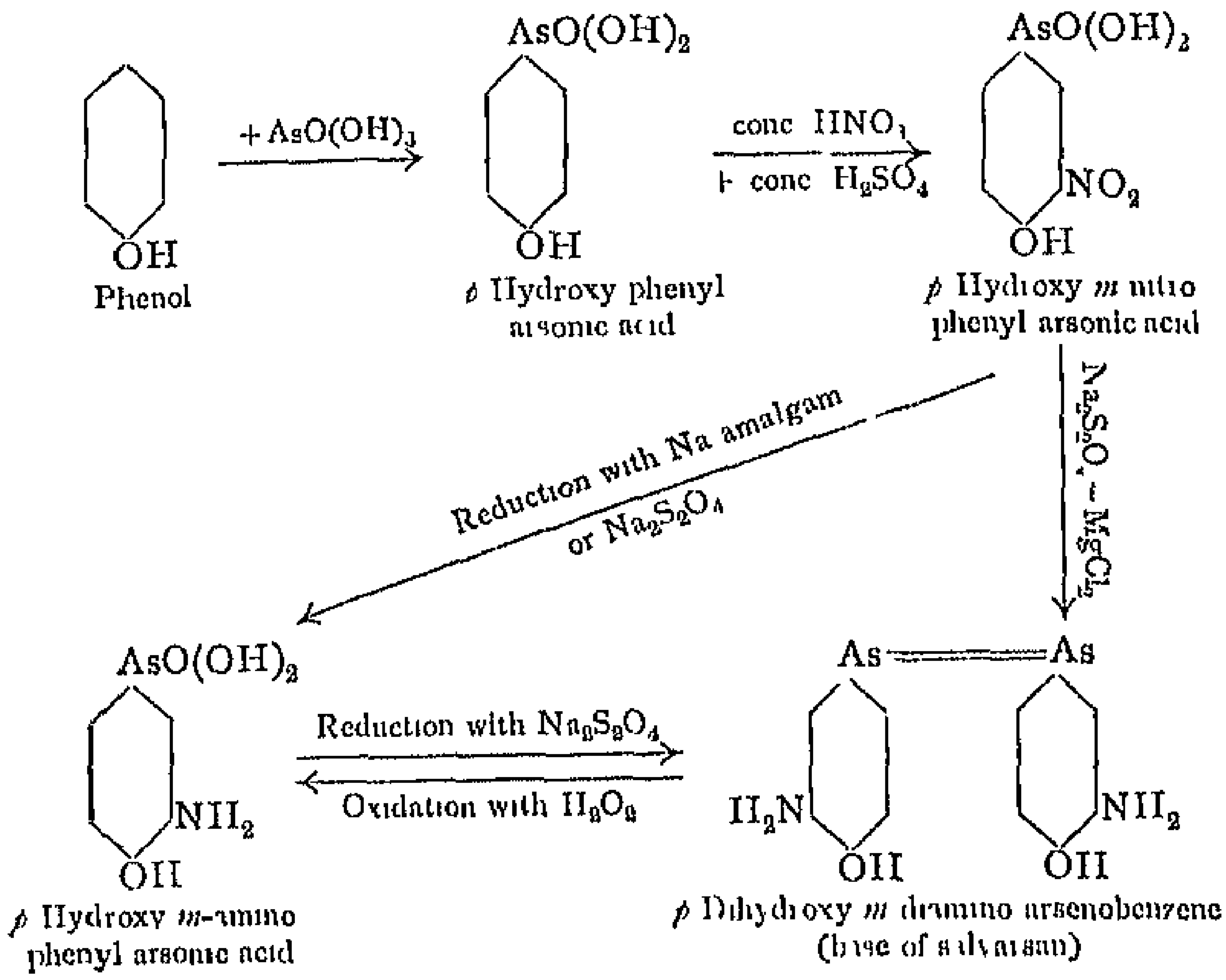
This compound can be prepared in a variety of ways, such as by the reduction of *p*-aminophenyl arsonic acid with sodium hydrosulphite, or with stannous chloride and hydriodic acid It melts at 260°, is insoluble in water and aqueous alkalis, but as a base is readily soluble in dilute hydrochloric acid Oxidising agents attack it rapidly, as the arseno compounds in general are characterised by strong reducing properties Diamino-arsenobenzene also gives the reactions of primary amines It is readily diazotised, converted into azo-dyes, and condensed with aldehydes

The reduction of *p*-aminophenyl arsonic acid to diamino-arsenobenzene is found to bring about a great increase in toxic power, in explanation of which it has been suggested that the chemoceptors of the parasites are able to attach themselves to the trivalent but not to the pentavalent arsenic residue[2] *pp'*-Diamino-arsenobenzene also possesses a much greater trypanocidal action The belief that only those radicals containing trivalent arsenic exert a direct trypanocidal action led to the examination of other arsenic compounds and the discovery of salvarsan

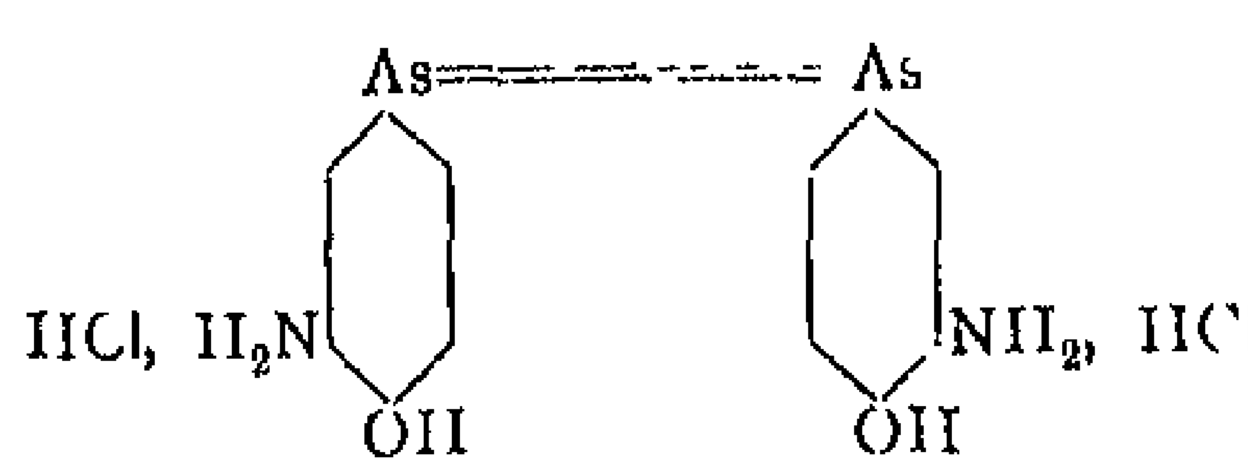
***p*-Dihydroxy-*m*-diamino arsenobenzene (Base of Salvarsan)** —This compound, the hydrochloride of which, under the name of salvarsan, has excited such general interest in the medical world, was prepared from *p*-hydroxy-phenyl-arsonic acid The latter was obtained directly from phenol and arsenic acid, in the same manner as phenol-sulphonic acid is obtained from phenol and sulphuric acid It was then nitrated,

[1] P Ehrlich and Bertheim, *Ber*, 1911, 44, 1260 [2] See, however, H H Dale, Presidential Address to Section I (Physiology), *B A Rep*, 1924

and the resulting *p*-hydroxy-*m*-nitrophenyl arsonic acid reduced as indicated in the following scheme



Dihydrochloride of *p* dihydroxy-*m* diamino-arsenobenzene, Salvarsan or "606"[1]



In the preparation of the dihydrochloride, the crude base obtained by the above process is dissolved in methyl alcohol containing the theoretical proportion of hydrochloric acid, and the mixture stirred with several times its volume of well-cooled ether All these and the following operations are, as far as possible, conducted in the absence of air The hydrochloride separates out as a microcrystalline precipitate and is filtered off under suction, washed with ether, and dried *in vacuo* over sulphuric acid and paraffin wax After this it is immediately sealed up in small tubes which are either evacuated to a high degree or filled with an indifferent gas

Salvarsan is a yellow, crystalline powder, readily soluble in water, methyl alcohol and glycerol, less readily soluble in ethyl alcohol

[1] Ehrlich and Bertheim, *Ber*, 1912, 45, 756

and insoluble in ether A point requiring careful attention in its practical use is that, like other arseno-compounds, it is readily oxidised When exposed to the air it rapidly acquires a proportion of the far more poisonous *amino hydroxy-phenylarsine oxide*[1] As an injection of such a preparation would be dangerous for the patient, salvarsan is preserved in evacuated tubes, or in ampoules which have first been exhausted and then filled with an indifferent gas

Salvarsan has proved a valuable specific for certain dangerous protozoal diseases, particularly syphilis, and has also been used with success in cases of *malaria tertiana*

Neosalvarsan —Dihydroxy-diamino-arsenobenzene, the base of salvarsan, condenses with formaldehyde sulphoxylate, when one or two of the sulphoxylate groups may enter the molecule The sodium salt of the compound containing one such group has been placed on the market under the name of "neosalvarsan" It possesses the advantage that when dissolved in water or physiological salt solution it is suitable for injection without further preparation Solutions of salvarsan, on the other hand, are acidic, and require to be neutralised with alkali immediately before injection

Metallic derivatives such as *copper salvarsan* and *silver salvarsan* also possess valuable therapeutic properties[2]

VIII

Phenols

Formation—The phenols are compounds in which hydrogen atoms of the benzene nucleus[3] have been replaced by hydroxyl groups According to the number of atoms substituted in this manner we speak of mono-, di- or trihydric phenols and so on The monohydric derivatives, in particular, are formed during the dry distillation of wood and coal Hence they are present in coal tar, from the carbolic oil of which they are prepared industrially (see p 412) Phenols may be prepared by the following methods —

1 By the fusion of sulphonic acids with sodium or potassium hydroxide[4] (p 406)

2 From diazonium salts by heating with water (see p 394) The sulphates are best employed for this reaction, since with nitrates the nitric acid set free may lead to the formation of nitrophenols

[1] Ehrlich and Bertheim, *Ber*, 1912, 45, 764 [2] P Karrer, *Ber*, 1919, 52, 2319 Binz, Bauer and Hallstein, *Ber*, 1920, 53, 416 [3] If the hydroxyl group enters into a side chain instead of the nucleus, an aromatic alcohol is formed (*e g*, benzyl alcohol, $C_6H_5 \cdot CH_2OH$) Compounds of this type are treated later [4] It should be remembered that, in the absence of other substituents, the monohalogen derivatives of benzene do not exchange halogen for hydroxyl when treated with alkali hydroxides, thus differing from the alkyl halides

3 By the action of oxygen on aromatic organo-magnesium compounds, and decomposition of the resulting product with dilute hydrochloric acid (see p 134)

Properties and Reactions—In their structure, as well as in many of their reactions, the phenols resemble the tertiary alcohols of the aliphatic series Like these they form esters, but show a characteristic distinction in their weakly acidic nature, due to the presence of the aromatic hydrocarbon radical This property is illustrated by the ease with which phenols dissolve in aqueous alkalis, with the formation of salts The phenols, however, are only weakly acidic, and their salts, unlike those of the carboxylic acids, are decomposed by carbon dioxide These facts are frequently utilised in the purification of phenols from neutral or more strongly acidic substances The acid character of the phenolic hydroxyl group is influenced by the entrance of other substituents into the nucleus, and is strengthened, for example, by the presence of nitro-groups

The hydrogen atom of the hydroxyl group may also be replaced by hydrocarbon radicals, with the formation of ethers These are prepared from metallic phenates by interaction with alkyl halides or salts of alkyl sulphuric acids

$$C_6H_5ONa + IC_2H_5 = C_6H_5\ OC_2H_5 + NaI$$

If the vapour of a phenol, alone or mixed with that of benzene, is led over thoria at 390° to 450°, the corresponding ether is produced, *e g* C_6H_5 O C_6H_5, from phenol itself Mixed ethers, such as C_6H_5 O CH_3, are obtained in the same manner from the mixed vapours of a phenol and an alcohol[1] Phenols are also quite easily phenylated by treating their alkali salts with phenyl bromide in the presence of copper as catalyst.

By the action of phosphorus pentachloride the hydroxyl group of a phenol can be replaced by chlorine, though less readily than in the case of the alcohols When heated with zinc dust, phenols are converted into the parent hydrocarbons The fact that the hydrogen atoms attached to the nucleus of a phenol are more easily substituted than those in the aromatic hydrocarbons has already been emphasised (see p 362) Most of the phenols give characteristic colour reactions with ferric chloride in aqueous solution

Certain other reactions which are peculiar to polyhydric phenols are described later

1 Monohydric Phenols and their Derivatives

Phenol, *carbolic acid*, *Acidum carbolicum*, C_6H_5OH, is the chief constituent of that fraction of coal tar boiling at 170° to 230°, and generally known as middle or carbolic oil It is prepared from this source, after removal of naphthalene, by shaking out with dilute caustic

[1] Sabatier and Mailhe, *C r*, 1910, 151, 359, 492

soda The aqueous layer is run off and phenol precipitated with sulphuric acid or carbon dioxide Finally it is purified by distillation

The formation of phenol from aniline and other sources has been indicated above

In the pure form phenol is a white, crystalline substance of melting-point 43°, which gradually turns pink on keeping It is liquefied on addition of a very small proportion of water, and dissolves completely in 15 parts at 20° It possesses a peculiar pungent smell, is poisonous, and is employed in aqueous solution as a disinfectant

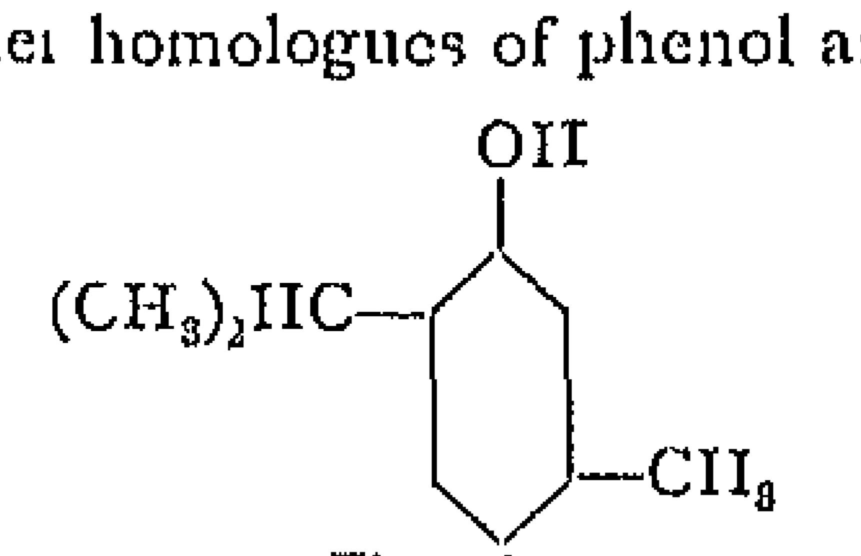
When treated with bromine it yields a white precipitate of 2 4 6-*tribromophenol*, a reaction which is used for its separation and quantitative estimation Phenol dissolves readily in alkali hydroxides with the formation of sodium and potassium phenates, these being obtained in the solid state when the solutions are evaporated Under special conditions carbon dioxide interacts with sodium phenate to give as final product sodium salicylate (see Salicylic Acid) This reaction is used in the commercial preparation of salicylic acid from phenol The electrochemical oxidation of phenol leads to the formation of catechol and hydroquinone [1]

HOMOLOGUES, ESTERS AND ETHERS OF PHENOL

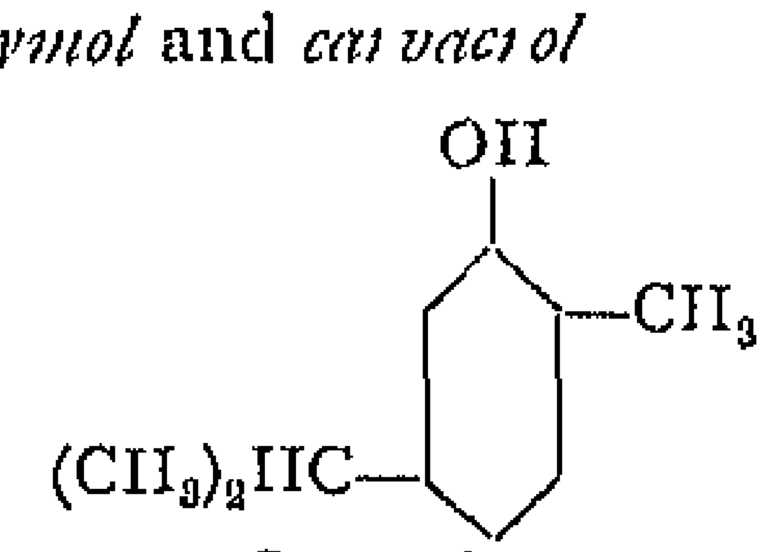
The **cresols**, $CH_3 \cdot C_6H_4 \cdot OH$, may be regarded as methyl derivatives of phenol or as hydroxy derivatives of toluene, they are found with phenol in coal tar The isomers are not isolated from this source in the pure state, but are usually placed on the market in the crude condition Since they are cheaper than phenol, they are much used as disinfectants [2]

The crude cresols are rendered soluble in water by the addition of resin soap or oil soap Preparations of this kind sold as disinfectants are *cresoline* and *lysol* The *three isomeric cresols* may be obtained in the pure state by the methods quoted on p 411 o-*Cresol* melts at 30° and boils at 191°, m-*cresol* melts at 4° and boils at 203° p-*Cresol* (m p 36°, b p 202°) is found among the putrefaction products of egg albumin

Other homologues of phenol are *thymol* and *carvacrol*



Thymol
(3-Methyl 6-isopropyl phenol)



Carvacrol
(2 Methyl 5 isopropyl phenol)

[1] Fichter, *Ber*, 1914, 47, 2003 *Helv Chim Acta*, 1919, 2, 583 [2] 4 n *Amyl* m *cresol* has been found to combine comparatively low toxicity with a high germicidal value (Coulthard, Marshall and Pyman, *J C S*, 1930, 281)

Thymol occurs together with cymene, $C_{10}H_{14}$, and thymene, $C_{10}H_{16}$, in oil of thyme, from which it is isolated by treating the oil with caustic soda and precipitating the solution with hydrochloric acid. It forms large crystals, m.p. 44° and b.p. 230°, which smell of thyme. It is used as a mouth-wash and in the treatment of wounds. **Carvacrol**, present in *Origanum hirtum*, is obtained from its isomeride carvone, found in carraway oil, by heating with glacial phosphoric acid, or from camphor by heating with iodine. It melts at 0° and boils at 236°.

Esters of phenols are produced by the action of acid chlorides or anhydrides on phenols or their alkali salts. Like the esters of aliphatic alcohols they are decomposed into their components when heated with alkalis. The sulphuric and glycuronic esters of phenols and of many heterocyclic hydroxy compounds which are eliminated in the urine play an important part in the animal organism, since by union with acids the phenols lose their poisonous character.

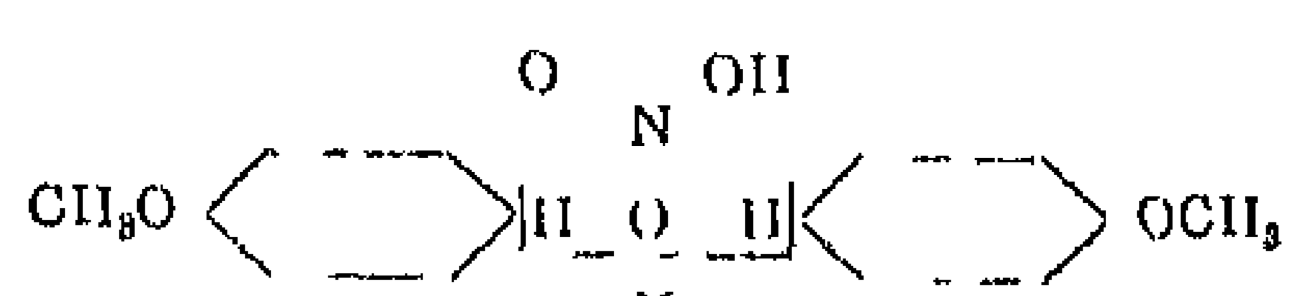
Phenylsulphuric acid, *phenolsulphuric acid*, $C_6H_5.O.SO_3H$, is unknown in the free state. The potassium salt occurs in urine, and may be prepared from potassium phenate by heating it with potassium pyrosulphate. When heated in a sealed tube the salt isomerises into potassium *p*-phenolsulphonate, $C_6H_5.O.SO_3K \longrightarrow HO.C_6H_4.SO_3K$. *Phenyl acetate*, $C_6H_5.O.COCH_3$, boils at 195°.

Ethereal derivatives of phenol are obtained in the same manner as from aliphatic compounds, by the action of phenates on alkyl halides:

$$C_6H_5.O.Na + I.CH_3 = C_6H_5.O.CH_3 + NaI$$

It has already been stated that aromatic halogen derivatives react less readily than those of the aliphatic series, and the purely aromatic ethers, such as $C_6H_5.O.C_6H_5$, can only be prepared by the above reaction in the presence of finely-divided copper as catalyst. Phenolic ethers are exceedingly stable substances. Those containing an aliphatic radical are only decomposed by prolonged heating with alcoholic potash or hydriodic acid, $C_6H_5.OCH_3 + HI = C_6H_5.OH + CH_3I$. When treated with nitric acid,[1] two reactions proceed concurrently, viz., nitration of the ether I, and conversion into derivatives of diphenyl nitric acid (diphenyl hydroxylamine oxide) II.

I



II

Phenyl methyl ether, **anisole**, $C_6H_5.O.CH_3$, is a colourless liquid, b.p. 155°, which resembles the ethyl ether, **phenetole**, $C_6H_5.O.C_2H_5$, b.p. 172°, in possessing a very characteristic smell. **Phenyl ether**, $C_6H_5.O.C_6H_5$, may be obtained from phenol by the dehydrating action of zinc chloride, $2C_6H_5OH = (C_6H_5)_2O + H_2O$, and also by warming benzene diazonium sulphate with phenol. It is best prepared by heating potassium phenate with bromobenzene in the presence of finely divided copper:

$$C_6H_5.OK + BrC_6H_5 \longrightarrow C_6H_5.O.C_6H_5 + KBr$$

It is a pleasant smelling substance, m.p. 28° and b.p. 253°, which is not hydrolysed by heating with hydriodic acid.

[1] K. H. Meyer and Billroth, *Ber.*, 1919, **52**, 1476.

SULPHONIC, NITRO-[1] AND AMINO-DERIVATIVES OF PHENOL

Ortho- and para-phenolsulphonic acids, $HO \cdot C_6H_4 \cdot SO_3H$, are formed when phenol dissolves in concentrated sulphuric acid. Under the influence of heat the *o*-compound passes into the *p*-compound. The potassium salt of the *p*-acid is also obtained by the isomerisation of the potassium salt of phenylsulphuric acid (see above). When *p*-phenolsulphonic acid is treated with iodine it yields 2 : 6-*diiodo-p-phenolsulphonic* acid, used as an antiseptic under the name of *Sozoiodol*. *m-Phenolsulphonic acid* is formed from *m*-benzene-disulphonic acid by the action of potassium hydroxide.

Phenol is very easily nitrated, and yields, according to conditions, mono-, di- or trinitrophenols, in which the nitro-group substitutes almost entirely in the *o*- and *p*-positions, and little or not at all in the *m*-position to the hydroxyl. Even dilute nitric acid can nitrate phenol. As has already been mentioned, the nitro-derivatives are more strongly acidic than phenol itself, and decompose carbonates.

o-Nitrophenol, $HO \cdot C_6H_4 \cdot NO_2$, forms yellow crystals, m.p. 45° and b.p. 214°. *p-Nitrophenol* forms colourless needles, m.p. 114. These isomers can be separated by distillation in steam, in which only the *o*-compound is volatile, the *p*-nitrophenol remaining behind. *m-Nitrophenol* is obtained by the diazotisation of *m*-nitraniline and is a yellow, crystalline substance, m.p. 96.

Picric acid, 2 : 4 : 6-*trinitrophenol*, $HO \cdot C_6H_2(NO_2)_3$, is a compound of great technical importance. It is prepared on the large scale by treating phenol (1 part) with sulphuric acid (4 to 6 parts of sp. gr. 1·84), the mixture being then added with stirring to concentrated nitric acid (7·5 parts of sp. gr. 1·38). During the addition the temperature is maintained at about 10°, after which the mixture is gradually warmed to about 80° to 90°, till gas evolution ceases. Picric acid crystallises out on cooling. It is filtered off or separated in a centrifuge, washed with water and recrystallised from hot water. Not more than three nitro-groups can be introduced into phenol by treatment with nitric acid.

Picric acid is also formed by the action of nitric acid on a great variety of organic substances, such as silk, wool, Peru balsam and indigo.

Picric acid crystallises in pale yellow leaflets of an intensely bitter taste. It is only sparingly soluble in cold water, and melts at 122°. In an acid bath it dyes silk and wool yellow, but the colour is not very fast.

Although not now used as a dye, picric acid is employed in large

[1] The tautomerism observed by Hantzsch (*Ber.*, 1906, 39, 1073, 1084) in the case of the esters of nitrophenols, and the light thus thrown on the constitution of the nitrophenols themselves, is discussed later in connection with the quinones. *Nitrosophenols* are described under oximes of quinone.

quantities as an explosive. When suddenly heated, or detonated by means of fulminate of mercury, the compound decomposes according to the equation

$$C_6H_2(NO_2)_3OH = 6CO + H + 3N + H_2O$$

Picric acid is one of the most powerful explosives, and is known by various names, *e.g.* **lyddite** in Great Britain, **melinite** in France. It is used as a filling for shells and as an explosive by sappers. During the last few decades, **trinitrotoluene** (T.N.T.), $C_6H_2(NO_2)_3CH_3$, has come into use as a filling for high explosive shells. While this compound is almost as powerful an explosive as picric acid, it is greatly superior to it in a number of other respects.

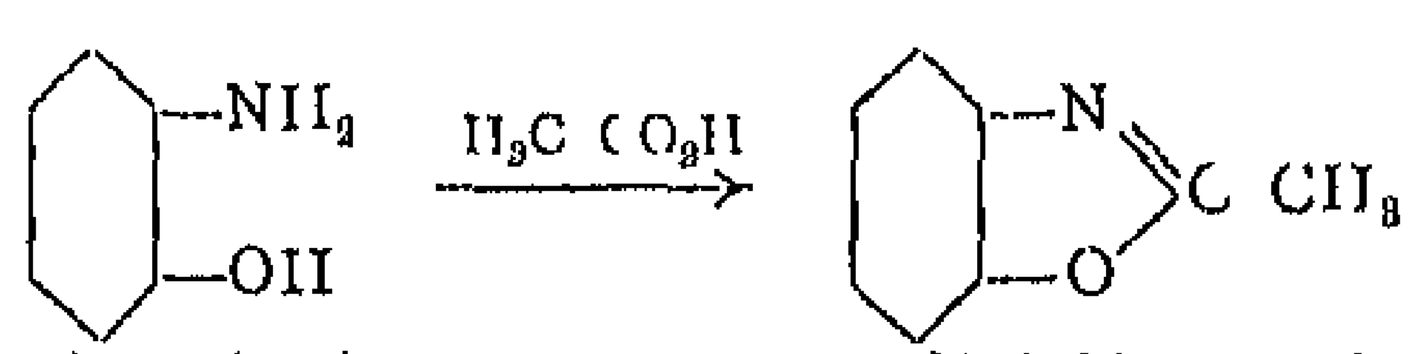
Characteristic among the chemical properties of picric acid are those due to its strongly acidic nature. When treated with phosphorus pentachloride, picric acid exchanges the hydroxyl group for chlorine and yields *picryl chloride*, $C_6H_2(NO_2)_3Cl$, m.p. 83°, which resembles the acid chlorides in its behaviour. With ammonia this compound is converted into *picramide*, $C_6H_2(NO_2)_3NH_2$, m.p. 188°. Potassium picrate, $C_6H_2(NO_2)_3OK$, and *ammonium picrate*, $C_6H_2(NO_2)_3ONH_4$, are as explosive as the free acid, although little use is made of them. When the silver salt is treated with ethyl bromide, it yields *trinitro-phenetole*, $(NO_2)_3C_6H_2\cdot OC_2H_5$, together with *aci*-trinitro-phenol ethyl ether,[1]

$$(NO_2)_2C_6H_2\genfrac{}{}{0pt}{}{\diagup O}{\diagdown NO\cdot OC_2H_5}$$

Picric acid unites with many aromatic hydrocarbons, such as naphthalene and anthracene, to form beautifully crystalline coloured addition compounds, which are sometimes of service in the recognition and isolation of these hydrocarbons.

On reduction the nitrophenols give aminophenols, in the same way as nitro-hydrocarbons yield amino-compounds. Aminophenols, as would be expected, are both acids and bases. In the free state they readily undergo decomposition, but the hydrochlorides are more stable.

o-*Aminophenol*, $NH_2\cdot C_6H_4\cdot OH$, melts at 170°, and its methyl ether, ***o*-anisidine**, $NH_2\cdot C_6H_4\cdot OCH_3$, is a liquid of b.p. 218°. Like the *o*-phenylene diamines, the *o*-aminophenols tend to form cyclic compounds, *e.g.* with carboxylic acids they yield *benzoxazoles*,



o Aminophenol

μ Methyl benzoxazole (Ethenyl aminophenol)

Diethyl-m-*aminophenol*, $(C_2H_5)_2N\cdot C_6H_4\cdot OH$, m.p. 87°, and *dimethyl*-m-*aminophenol*, $(CH_3)_2N\cdot C_6H_4\cdot OH$, are prepared by fusing together

[1] Hantzsch and Gorke, *Ber.*, 1906, 39, 1077.

diethyl or dimethylaniline *m* sulphonic acid and sodium hydroxide They are used for the manufacture of rhodamine dyes

p *Aminophenol*, m p 184°, is formed when *p*-nitrophenol is reduced with iron and hydrochloric acid, and is best prepared by the electrolytic reduction of nitrobenzene in strong sulphuric acid solution (see p 378) An alkaline solution of *p*-aminophenol, containing a little sodium sulphite, is sold as a photographic developer under the name of **rodinal** Its methyl derivative, CH_3 NH C_6H_4 OH, known as **metol**, is also used for the same purpose p-*Phenetidine*, NH_2 C_6H_4 OC_2H_5, the ethyl ether of *p*-aminophenol, is employed in the preparation of aceto-*p*-phenetidine or **phenacetine** (*p*-ethoxy acetanilide), CH_3CO NH C_6H_4 OC_2H_5, m p 135°, which is used as an antipyretic and in cases of neuralgia, and also in the preparation of **lactophenine** or lactyl-phenetidine and a number of other compounds

2 4-*Diaminophenol*, obtained from 2 4-dinitrophenol, is also of interest, as its sodium salt is employed as a photographic developer under the name of **amidol**

2 Dihydric Phenols and their Derivatives

In the main the di- and polyhydric phenols closely resemble the monohydric compounds in their properties, but many of them are strong reducing agents in alkaline solution They are generally prepared from the di- or polysulphonic acids of aromatic hydrocarbons, or from phenolsulphonic acids, by fusion with potassium hydroxide According to the relative positions of the two hydroxyl groups the dihydric phenols show characteristic differences in chemical behaviour

The *ortho*-compounds frequently give green colorations with ferric chloride, and readily yield heterocyclic derivatives in which the two hydrogen atoms of the hydroxyl groups are replaced by a divalent radical

The *meta*-compounds usually give a deep violet coloration with ferric chloride, and undergo the fluorescein reaction, *i e*, when heated with phthalic anhydride they yield *phthaleins*, which show a green fluorescence in alkaline solution [1]

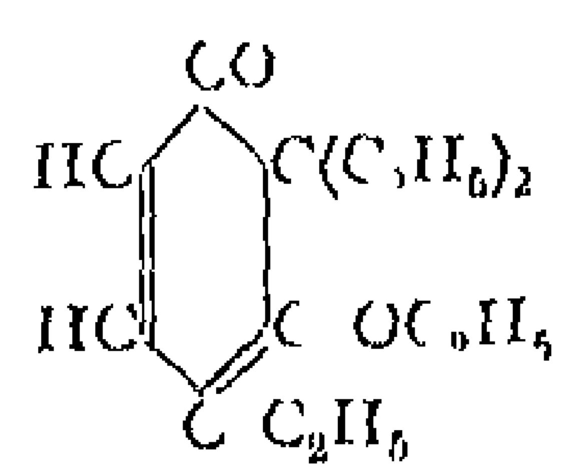
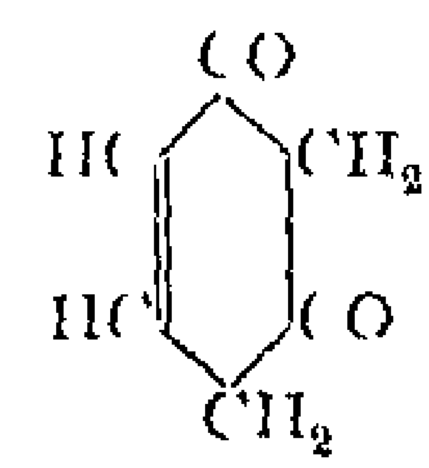
The *para* compounds on oxidation very easily pass into quinones, which are readily recognised

Catechol, *pyrocatechin*, o-*dihydroxy-benzene*, $C_6H_4(OH)_2$, m p 104°, occurs in living as well as in fossil plants Thus it has been obtained from catechin, moringatannic acid, kinotannic acid and other sources containing tannic acids, and has been shown to be present in crude wood tar, crude beet sugar, and the tar waters from bituminous shale and coal It is formed by oxidising phenol with hydrogen peroxide, and from *o*-benzenedisulphonic acid or *o*-phenolsulphonic acid by fusion with alkali The monomethyl ether, *guaiacol*, HO C_6H_4 OCH_3,

[1] This reaction is hindered by substitution in the meta position to the two hydroxyl groups

occurs in the crude creosote of beech tar. An aqueous solution of catechol gives a green colour with ferric chloride, which changes to deep red on the addition of alkalis, alkali carbonates or ammonia. The red colour is due to the formation of the complex $[Fe(C_6H_4O_2)_3]H_3$, which in alkaline solution gives a red anion. Other phenols and phenol-carboxylic acids also give deep colorations with ferric chloride in alkaline solution. A very important derivative of catechol is adrenaline (p. 671).

Resorcinol, m-*dihydroxy-benzene*, $C_6H_4(OH)_2$, m.p. 119°, is prepared technically by fusing benzene disulphonic acid with alkali at 235° to 270°. It crystallises in rhombic prisms or plates, which readily dissolve in water, alcohol or ether, and give a deep violet coloration with ferric chloride. It yields fluorescein on being heated with phthalic anhydride, and is used in the preparation of dyes. With cold nitric acid it yields a trinitro-derivative known as *styphnic acid*, m.p. 175°, which is also formed by treating various gum-resins with nitric acid. It has been shown[1] that the action of ethyl iodide and potassium hydroxide on resorcinol leads to the formation of resorcinol diethyl ether, accompanied by not inconsiderable amounts of tri- and tetraethyl derivatives of resorcinol. The latter compound possesses the structure I,

I  II 

thus proving that, during the ethylation, part of the resorcinol reacted in the keto-enolic form. In other words, we have here an example of the *tautomerism of resorcinol*. Resorcinol combines with sodium bisulphite to give a product which is in all probability the bisulphite compound of 3 : 5-*diketo-hexamethylene*-1-*sulphonic acid*. The formation of this substance may be explained[2] on the assumption that it is derived from the tautomeric form of resorcinol, II.

n-**Hexylresorcinol**, *Caprokol*, (OH : OH : C_6H_{13} = 1 : 3 : 4), is a valuable internal antiseptic of high germicidal value[3] (*cf.* p. 351).

Hydroquinone, *quinol*, p-*dihydroxy-benzene*, m.p. 169°, is prepared by reducing quinone with sulphurous acid, and by virtue of its reducing properties is used as a photographic developer. With oxidising agents it is easily converted into quinone. Sodium bisulphite unites with hydroquinone to give 1 : 4-*dihydroxy-hexamethylene*-1 : 2 : 4-*trisulphonic acid*.[4] This reaction, as well as certain changes which take place in

[1] Herzig and Zeisel, *Monats.*, 1890, 11, 291; 1893, 14, 376; *Ber.*, 1920, 53, 518; 1921, 54, 1403. [2] W. Fuchs and Elsner, *Ber.*, 1920, 53, 886; 1924, 57, 1225. [3] Johnson and Lane, *J.A.C.S.*, 1921, 43, 348; Dohme, Cox and Miller, *ibid.*, 1926, 48, 1688. [4] W. Fuchs and Elsner, *Ber.*, 1919, 52, 2281.

the hydroquinone developer, are explained by the assumption that hydroquinone may also react in tautomeric form as an unsaturated cyclic ketone.

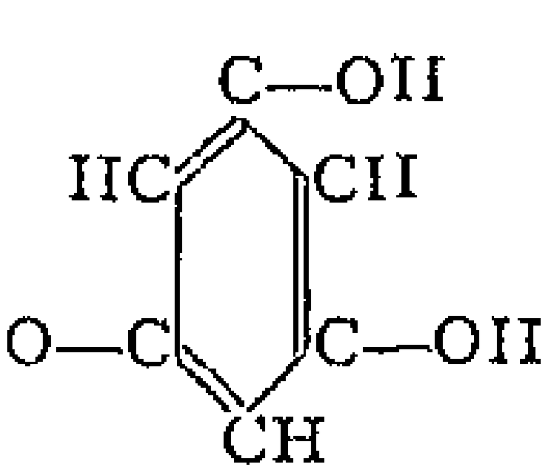
Of the six dihydroxy-toluenes, $CH_3 \cdot C_6H_3(OH)_2$, the most important is **orcinol**, 3 : 5-*dihydroxy-toluene*, which may be regarded as a homologue of resorcinol. It occurs in the free and combined state in many lichens of the Roccella and Lecanora families, and may be obtained from *orsellinic acid* by boiling with lime, or synthetically from acetone-dicarboxylic ester. Orcinol crystallises with 1 mol. H_2O in colourless prisms, m.p. 107° and b.p. 290°. When exposed to the air in ammoniacal solution it is transformed into *orcein*, $C_{28}H_{24}N_2O_7$, a reddish-brown amorphous powder which forms the chief constituent of the dye *orseille* (French purple). Closely related to orcein is the dye *litmus*, which is also prepared from lichens of the above varieties.

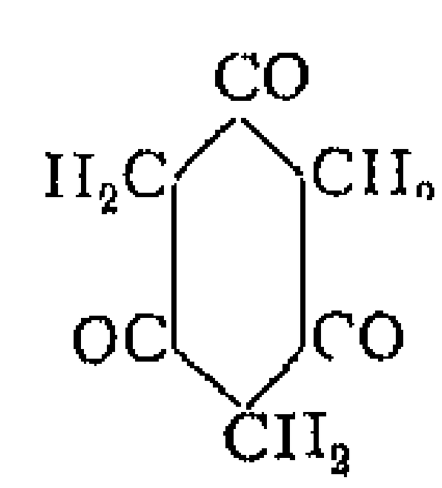
3. Trihydric Phenols and their Derivatives

All of the three possible isomerides expected on theoretical grounds are known, viz., pyrogallol, phloroglucinol and hydroxy-hydroquinone.

Pyrogallol, *pyrogallic acid*, 1 : 2 : 3-*trihydroxy-benzene*, is prepared by heating gallic acid, $C_6H_2(OH)_3 \cdot COOH = C_6H_3(OH)_3 + CO_2$. It forms white plates, m.p. 132°, which dissolve readily in water. In alkaline solution it turns brown owing to absorption of oxygen, and hence is sometimes used for estimating oxygen in gas analysis.[1] Owing to its reducing properties it is also employed as a developer in photography.

Phloroglucinol, 1 : 3 : 5-*trihydroxy-benzene*, $C_6H_3(OH)_3$, melts at 218°, and is obtained as a disruption product of certain complex substances, *e.g.* from many resins by fusion with potash. It is best prepared from symmetrical triamino-benzene by heating with acids. Synthetically it may be obtained by Baeyer's method from sodio-malonic ester, which readily condenses to *phloroglucinol tricarboxylic ester*, $C_6(OH)_3(COOC_2H_5)_3$, and this on heating with alkalis yields phloroglucinol. Phloroglucinol is a tautomeric compound, reacting not only in the phenolic form, I., but also as a hexamethylene triketone, II.

I. 

II. 

Thus as a phenol it yields a trimethyl ether, $C_6H_3(OCH_3)_3$, and a triacetyl derivative, $C_6H_3(O \cdot CO \cdot CH_3)_3$, and as a ketone it forms a trioxime, $C_6H_6(NOH)_3$.

[1] For the chemical changes occurring during this reaction see Harries, *Ber.*, 1902, 35, 2954.

Hydroxy hydroquinone, 1 2 4 *trihydroxy benzene*, m p 140, is produced in small amount when hydroquinone is fused with caustic soda Its triacetate is easily obtained by warming quinone with acetic anhydride and concentrated sulphuric acid

4 Polyhydric Phenols

Of these, only **hexahydroxy benzene**, $C_6(OH)_6$, need be mentioned The potassium salt of this compound, $C_6(OK)_6$, better known as potassium carbonyl is obtained by leading carbon monoxide over heated potassium, and is also formed during the preparation of potassium from charcoal and potassium carbonate, when it occasionally gives rise to explosions With hydrochloric acid the potassium salt yields hexahydroxy benzene, a white crystalline substance which readily undergoes oxidation

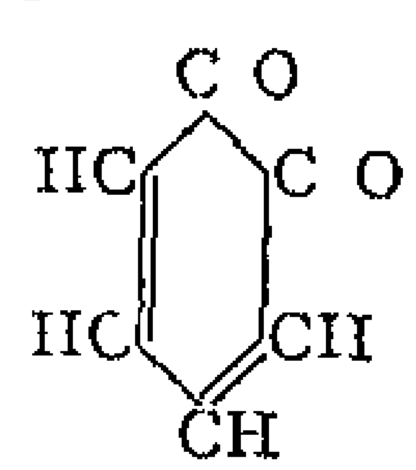
Corresponding to the thioalcohols and the alkyl sulphides are the **thiophenols**, *e g* C_6H_5 SH, and the **phenyl sulphides** They are of little importance and cannot be described here

IX

Quinone and Quinonoid Derivatives

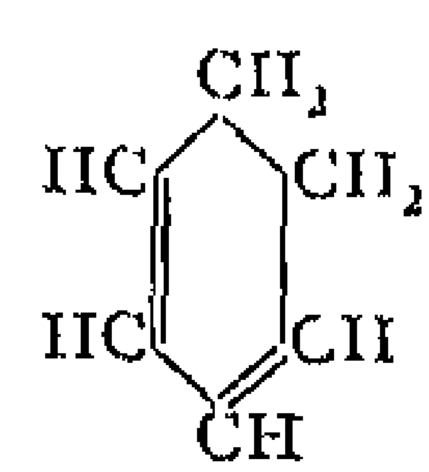
By quinones are understood compounds in which two hydrogen atoms of the benzene nucleus are replaced by two oxygen atoms, the products being distinguished as *o*- and *p*-quinones according to the relative positions of the substituents Up to the present no *m* quinone has been isolated,[1] and *o* quinones of benzene and its alkyl and halogen derivatives have only been prepared in rare cases and for the most part within recent years For this reason the *p*-compounds, which were the first to be discovered, were described shortly as quinones, and the name is still generally employed in this sense The constitution of the benzoquinones is expressed in the formulæ I and II below, and that of

I

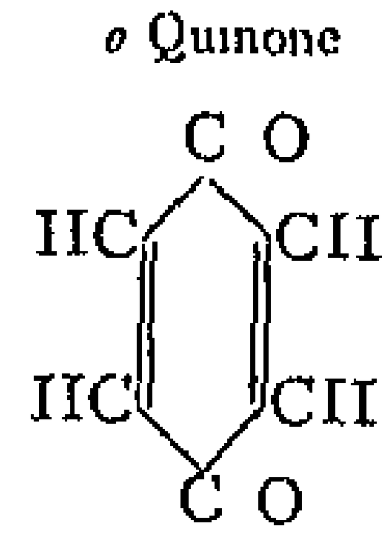


o Quinone

Ia

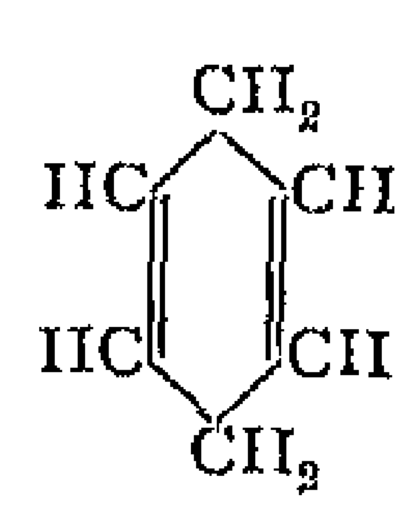


II



p Quinone

IIa



[1] Nevertheless it is probable that compounds of the *m* quinonoid type are capable of existence, see Hantzsch, *Ber*, 1906, 39, 1095, O Stark, *Ber*, 1913, 46, 2542 Whether the tribromo resoquinone described by R Meyer and Desamari (*Ber*, 1908, 41, 2437) is actually an *m* quinone, as assumed by the authors, requires further proof

other quinones in a similar manner It will be seen that they are represented as diketo-derivatives of an *o*- or *p*-dihydrobenzene (see I*a* or II*a*)

o-**Benzoquinone**, *o*-**quinone**,[1] is obtained when catechol is oxidised with silver oxide It exists in two solid modifications, one labile and crystallising in bright green needles, the other stable and crystallising in red, transparent plates[2] Probably we are here dealing with dimorphous forms of the same substance, which are identical in solution but, owing to a difference in crystal structure, exhibit different colours in the solid state *o*-Quinone is odourless and non volatile It decomposes on standing, and is reduced to catechol on treatment with sulphurous acid

p-*Quinones or quinones*, of which the simplest representative is ordinary quinone, are formed by the oxidation of various para-disubstitution products of aromatic hydrocarbons Most of them are yellow compounds of pungent smell, and are volatile in steam They are readily reduced, taking up two atoms of hydrogen to form hydroquinones They combine with two molecules of a monohydric phenol to give *phenoquinones*, and with one molecule of a dihydric phenol to yield dark coloured addition compounds such as *quinhydrone* (see below)

Quinone, *benzoquinone*, $C_6H_4O_2$, was first obtained by the distillation of quinic acid with manganese dioxide and sulphuric acid, and is also formed by the oxidation of many *p*-disubstitution products of benzene (*e g*, *p*-aminophenol, sulphanilic acid) It is usually prepared by oxidising aniline with sodium dichromate and sulphuric acid Quinone forms golden-yellow crystals, m p 166°, possessing a peculiar, pungent smell, it is volatile in steam, colours the skin brown and is poisonous With a great variety of substances it unites to form addition products,[3] *e g* with hydroquinone it yields **quinhydrone**, $C_6H_4O_2$, $C_6H_4(OH)_2$ The latter crystallises in green prisms of metallic lustre, and occurs as an intermediate product in the reduction of quinone and the oxidation of hydroquinone, on further reduction it is transformed into hydroquinone, and on oxidation into quinone

A volumetric estimation of quinones by means of titanous chloride is based on their ease of reduction[4], in the case of quinone the reaction proceeds according to the equation

$$C_6H_4O_2 + 2TiCl_3 + 2HCl = C_6H_4(OH)_2 + 2TiCl_4$$

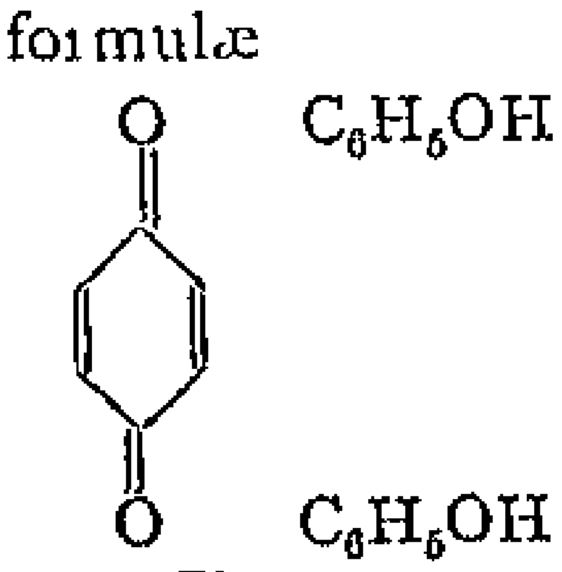
The quinone is dissolved in water and treated with an excess of standard titanous chloride solution, after which the unused titanous chloride is titrated with iron alum, using potassium thiocyanate as indicator

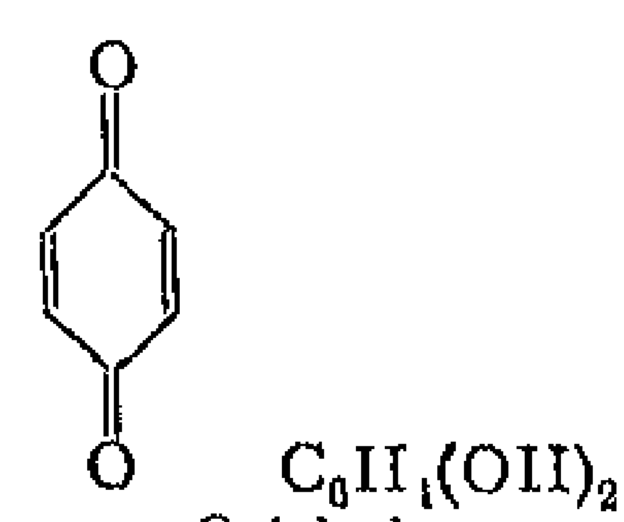
Tetrachloroquinone, **chloranil**, $C_6Cl_4O_2$, is produced by the chlorination of quinone, and also from a number of aromatic substances, such as phenol, by the action of chlorine or of potassium chlorate and hydrochloric acid It is employed as an oxidising agent in the manufacture of dyes

[1] Willstätter, *Ber*, 1904, 37, 4744 [2] Willstätter, *Ber*, 1908, 41, 2580, 1911, 44, 2171 Kehrmann and Cordone, *Ber*, 1913, 46, 3009 S Goldschmidt and F Graef, *Ber*, 1928, 61B, 1858 [3] For addition products of phenols and quinones, see K H Meyer, *Ber*, 1909, 42, 1149, 1910, 43, 157 W Schlenk, *Ann*, 1908, 363, 313, 1909, 368, 271, 295 [4] E Knecht and Hibbert, *Ber*, 1910, 43, 3455 See also Willstätter and Majima, *Ber*, 43, 1171

The Quinhydrones[1]

The simplest member of this group is the above-mentioned quinhydrone (Wohler, 1884), the constitution of which has given rise to much discussion It is now almost generally agreed that the quinhydrones are to be classed as molecular compounds This view is confirmed more particularly by the work of Pfeiffer, from which it appears that in the quinhydrones the carbonyl oxygen atoms of the quinonoid components are united to the unsaturated carbon atoms of the benzenoid components Since practically all quinhydrones, as well as the phenol-ether and hydrocarbon compounds of the quinones, are composed of 1 mol quinone and 1 or 2 mols of a benzenoid derivative, we are led to the assumption that each carbonyl oxygen atom can link up to one benzenoid molecule, as indicated in the following formulæ


Phenoquinone


Quinhydrone

The union is effected in such a manner that the subsidiary valency of the oxygen atom is saturated by a uniform field of affinity, which is produced by all, or at all events by the majority, of the unsaturated carbon atoms of the benzene derivative

This conception enables us to represent graphically the close relationship existing between quinhydrones, the coloured molecular compounds of nitro-derivatives, and the coloured additive compounds formed by ketones with acids and metallic salts

Quinhydrones	$R_2C{=}O$	C_nH_m	Molecular Compounds of Nitro derivatives	$R.NO_2$	C_nH_m
	$R_2C{=}O$	C_nH_{m-1} OH		$R.NO_2$	C_nH_{m-1} OH
	$R_2C{=}O$	C_nH_{m-1} NH_2		$R.NO_2$	C_nH_{m-1} NH_2

Halochromic Systems	$R_2C{=}O$	HX
	$R_2C{=}O$	MeX

The connecting link between these organic molecular compounds and similar inorganic complexes is provided by the compounds formed by ketones with metallic salts The latter stand in the closest relationship to two of the best-known groups of inorganic compounds of this type, viz, the double salts and the metallic ammines

$R_2C{=}O$		KCl		Am[2]	
	$SnCl_4$		$SnCl_4$		$SnCl_4$
$R_2C{=}O$		KCl		Am	

[1] Compare P Pfeiffer, *Organische Molekülverbindungen*, edited by J Schmidt (Enke, Stuttgart, 1927) [2] Am = ammine.

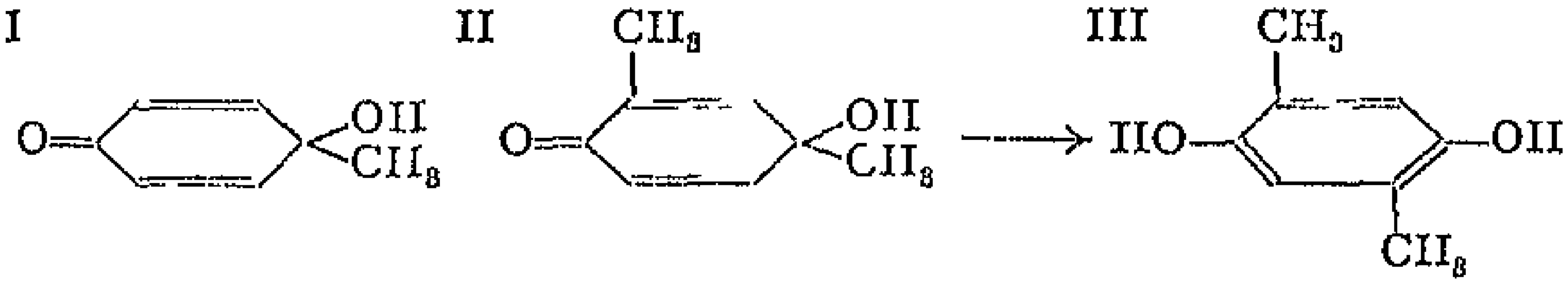
QUINONOID COMPOUNDS

From *o*- and *p*-quinones[1] are derived a number of coloured substances, which are formed by the replacement of hydrogen or the ketonic oxygen by monovalent or polyvalent atoms or groups Such compounds, which still contain the arrangement of linkings characteristic of the quinones (formulæ I and II, p 420) are said to have a quinonoid structure In spite of the non-existence of *m*-quinones, compounds of the *m* quinonoid type appear to exist under certain conditions[2]

For many reasons quinonoid compounds have attracted a considerable amount of attention from chemists They are of importance not only in practice, for example many dyes belong to this class, but also from the theoretical standpoint All these substances have a great tendency to change over from the quinonoid to the aromatic type (containing a benzene nucleus with three double bonds), and this tendency frequently leads to remarkable movements of the side chains in the molecule Thus it has been shown that the transformation of the quinol complex I into the corresponding aromatic structure may take place, according to experimental conditions, by the migration of either the hydroxyl or methyl group to another position in the nucleus

For example, 2 4-*dimethyl-quinol* II isomerises into p *xylohydroquinone* III

I II III



Quinone-imines

These are derived from quinones by replacing one or both of the ketonic oxygen atoms by the imino-group NH, or the alkyl- or aryl-imino group NR The simplest representatives of the class, *quinone-imine* (I) and *quinone-diimine* (II), have been prepared by Willstätter[3]

I II

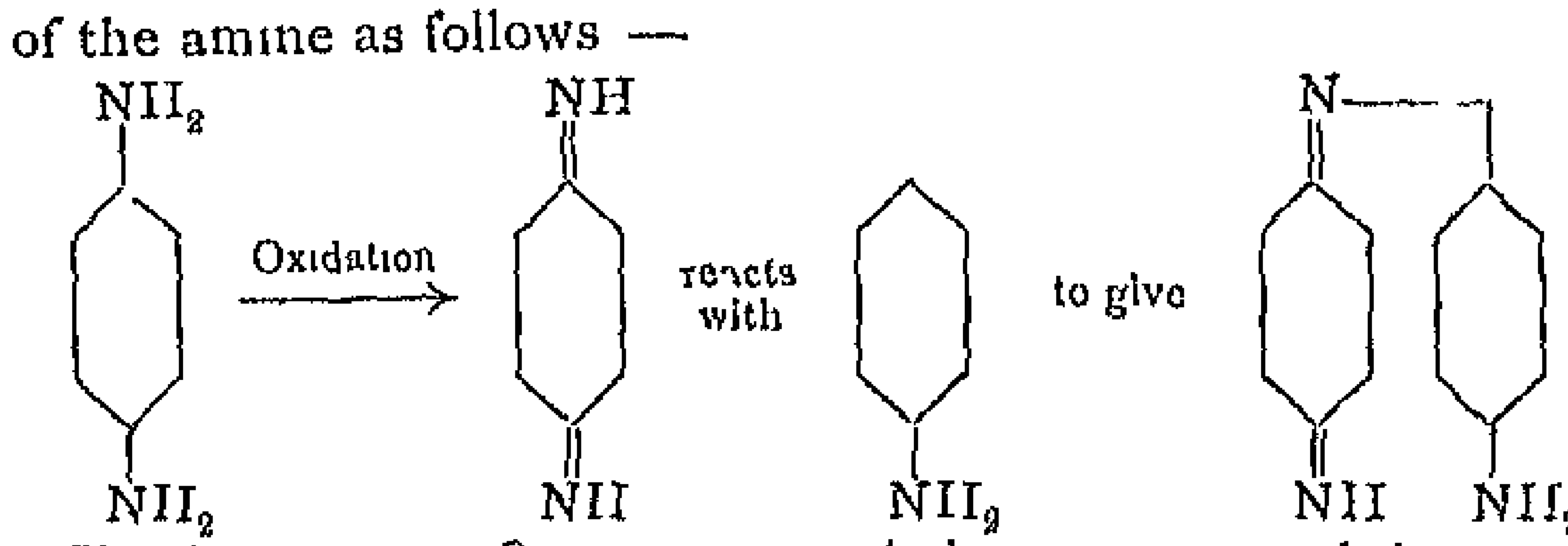
[1] The intense colour of these compounds may be ascribed to the fact that they are composed of four chromophore groups (see p 73), viz, two C=C groups and two C=O groups [2] Hantzsch, *Ber*, 1906, 39, 1095 O Stark and Garben have described a hydrocarbon crystallising in yellow needles, obtained from isophthalic ester and phenyl magnesium bromide From its method of formation and properties this is described as *m* quinonoid in structure and formulated as tetraphenyl-*m* xylylene, $C_{32}H_{24}$ *Ber*, 1913, 46, 659, 2252, 2542 [3] *Ber*, 1904, 37, 1494, 4605, *Ber*, 1905, 38, 2244

Quinone imine (I) is obtained by the oxidation of *p* aminophenol with silver oxide, $NH_2 \cdot C_6H_4 \cdot OH + O = NH : C_6H_4 : O + H_2O$. It forms colourless crystals smelling like quinone, which rapidly darken in colour. It is extraordinarily unstable and decomposes rapidly on lying in air. On warming for a short time with dilute sulphuric acid it is hydrolysed to quinone and ammonia. With stannous chloride and hydrochloric acid it is reduced to *p* aminophenol. **Quinone diimine** (II) is formed in similar manner by the oxidation of *p* phenylene diamine, and by the reduction of quinone dichloro diimine. It crystallises in colourless needles, melting about 124°, which are very unstable. With stannous chloride in acid solution it is readily reduced to *p* phenylene diamine, and with dilute sulphuric acid it yields quinone and ammonia.

As already mentioned, both the above imines are colourless in the crystalline state, and by comparison with quinone and the fulvenes (p. 351) it would appear that, in contradiction to the view long held,[1] the group C : NH is a weaker chromophore than C : O or C : C.

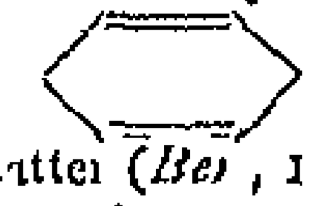
Quinone-diimine is the parent substance of large classes of dye-stuffs, chief among which are the indamines and the azines.[2] Recently certain other types of dyes, particularly in the diphenyl- and triphenyl-methane series (to be dealt with later), have also been formulated in the same manner as the quinone-imines.

Indamines are most readily prepared by oxidising mixtures of monamines and *p*-diamines, or by the interaction of amines and quinone dichloro diimine,[3] $ClN : C_6H_4 : NCl$. In the former reaction it may be supposed that quinone-diimine is first produced, which then in the course of further oxidation reacts with the *p*-hydrogen atom of the amine as follows:—



p Phenylene diamine — Quinone diimine — Aniline — Indamine

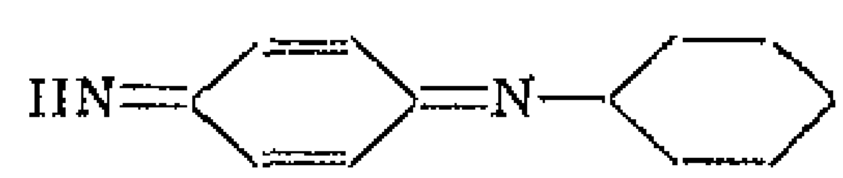
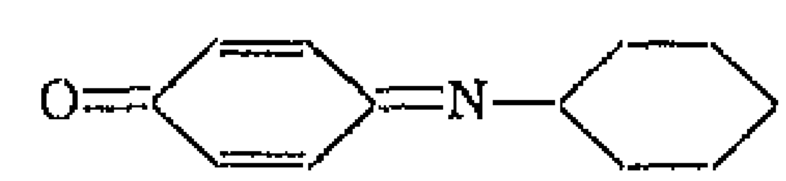
In confirmation of this, it is found that quinone-imine salts yield with amines intensely coloured solutions of indamines.

[1] The investigation of the quinone imines has also led to the discovery that certain quinonoid compounds can exist in both coloured and colourless forms (Willstatter, *Ber.*, 1905, **38**, 2244; Willstätter and Piccard, *Ber.*, 1908, **41**, 1458). In addition it is remarkable that whereas the simplest quinone imines are colourless and give colourless salts, all the alkyl derivatives of *p* phenylene diamine yield intensely coloured oxidation products which react as quinonimonium salts of the type of HN  $N(CH_3)_2Cl$. Baeyer (*Ber.*, 1905, **38**, 569; *Ann.*, 1907, **354**, 163), and also Willstätter (*Ber.*, 1908, **41**, 1468), suggest that colour is produced in organic compounds by the oscillation of some of the constituent atoms. [2] For the simplest quinonoid dyes, see J. Piccard, *Ann.*, 1911, **381**, 351. [3] **Quinone chlorimine**, $O : C_6H_4 : NCl$, and the above **dichloro diimine** are best prepared by the oxidation of *p* aminophenol hydrochloride or *p* phenylene diamine by means of hypochlorite solution.

Indamines are also formed by the action of nitroso-dimethylaniline on amines

Indamine, or **phenylene blue** (formula, see above), is obtained by the oxidation of an equimolecular mixture of *p* phenylene diamine and aniline, and is the simplest representative of the indamines. It forms greenish blue salts, most of which are soluble in water, and with reducing agents is converted into *p* diamino diphenylamine. *Tetramethyl indamine*, $C_{16}H_{19}N_3$, is obtained in a similar manner from dimethyl *p* phenylene diamine and dimethylaniline. Its salts also dissolve to give green solutions, the hydrochloride being known as Bindschedler's Green.

The **indophenols** are closely related to the indamines, and are obtained by oxidising mixtures of phenols with *p* diamines or *p* aminophenols, or by the action of nitroso dimethylaniline on phenols. Whereas indamines are amino derivatives of phenyl quinone diimine I, indophenols are amino derivatives of phenyl quinone imine II.

I  II 

The only members of this class used technically as dyes are those prepared from *p* phenylene diamine in combination with phenol or *a* naphthol. The latter is known as *a naphthol blue*.

Certain heterocyclic compounds which give rise to important dye stuffs, such as *phenazine* and *acridine* (see p 661), may also be formulated as quinonoid derivatives.

Nitrosophenols and Quinonoximes

p-Nitrosophenols may be obtained by the following methods —

1 By the action of nitrous acid on phenols.

2 By boiling *p*-nitroso-alkylamines with alkalis, *e g*,

$$ON\,C_6H_4\,N(CH_3)_2 + KOH = ON\,C_6H_4\,OK + HN(CH_3)_2$$

3 By the interaction of hydroxylamine hydrochloride with quinones in aqueous or alcoholic solution.

These methods of preparation indicate the possibility of two constitutional formulæ for the nitrosophenols, *e g* for *p*-nitrosophenol,

$HO\,C_6H_4\,NO$	$O\,C_6H_4\,N\,OH$
p Nitrosophenol	Quinone monoxime

The nitroso formula is supported by methods 1 and 2 and also by the fact that nitric acid oxidises the nitrosophenols to nitrophenols.

On the other hand, the quinonoxime formula provides the best explanation of method 3, and of a number of other properties and reactions of the nitrosophenols, such as their weak basic character, the formation of quinone dioximes, *e g* $C_6H_4(NOH)_2$, when they are treated with hydroxylamine hydrochloride, and their conversion on methylation into methyl ethers of quinonoximes.

For these reasons it is assumed that we are here dealing with a case of tautomerism. Probably the free compounds correspond to the nitrosophenol formula, while their salts possess the oxime structure.

Methyl ethers of true nitrosophenols have been prepared by A Baeyer and E Knorr,[1] who found that anisidine could be oxidised

[1] *Ber*, 1902, 35, 3034

by Caro's acid to give nitroso-anisole, *i.e.*, the methyl ether of the true nitrosophenol, a reaction similar to the oxidation of aniline to nitrosobenzene by means of the same reagent

$$C_6H_4\begin{cases}NH_2\\ O\cdot CH_3\end{cases} \longrightarrow C_6H_4\begin{cases}NO\\ O\cdot CH_3\end{cases}$$

The *p*-compound has never yet been prepared entirely free from *p*-nitro anisole, which is formed at the same time On the other hand, *o*-**nitroso anisole** is known in the pure state When hydrolysed with a solution of acid potassium sulphate it yields *o*-**nitrosophenol** In its reactions the latter strongly resembles *p*-nitrosophenol and hence is probably identical with the monoxime of *o*-quinone

Hydroxy-azo compounds and Quinone Phenylhydrazones

p-Hydroxy azobenzene and other similar compounds are regarded as tautomeric substances, in no simple case has it been found possible to isolate both desmotropic forms Both types, viz, the quinone phenylhydrazone and the hydroxy azo compound, exist, however, in a series of derivatives Thus the acyl derivatives of *p*-hydroxy azobenzene and the corresponding isomeric acylated quinone phenylhydrazones are both known, and are formed by the action of unsymmetrical acyl phenylhydrazines on benzoquinone Quinone benzoyl phenylhydrazone has been shown to undergo a peculiar intramolecular change when shaken in dry ethereal solution with powdered potassium hydroxide[1] Under these conditions the benzoyl group moves to the oxygen atom standing in the *p* position to the further nitrogen atom

$$\underset{CO\cdot C_6H_5}{C_6H_5\cdot N}—N:C_6H_4:O \longrightarrow C_6H_5\cdot N:N\cdot C_6H_4\cdot \underset{CO\cdot C_6H_5}{O}$$

This reaction appears to be a general one with acylated quinone phenylhydrazones Similar changes have been shown to occur with *o*-quinonoid derivatives of this type[2] Since, then, the system I is immediately transformed into II,

$$\text{I}\quad \underset{O}{—C}—\underset{|}{C}:N\cdot \underset{Ac}{N}\cdot R \qquad\qquad \text{II}\quad \underset{O\cdot Ac}{—C}\quad \underset{|}{—C}:N\cdot N\cdot R$$

it would be contrary to all experience of tautomeric and desmotropic substances to assume that the parent compounds, *i.e.*, the hydrogen derivatives, should be stable in the quinonoid form Hence it is concluded that *all the parent hydroxy azo compounds of this series, together with their ethers and esters, are true benzenoid azo derivatives* It is only by using indirect methods that the quinonoid forms of a few of these compounds have been isolated, and of these only acyl derivatives of the *p*-series are known with certainty

Tautomerism of the Nitrophenols

It has been shown by Hantzsch that *ethers of the nitrophenols* exist in two series, corresponding to the following formulæ

$$Ar\begin{cases}NO_2\\ OC_nH_{2n+1}\end{cases} \qquad\qquad Ar\begin{cases}NO\cdot OC_nH_{2n+1}\\ O\end{cases}$$

True nitrophenolic ethers (benzenoid and colourless) — *aci* Nitrophenolic ethers (quinonoid and coloured)

[1] R Willstätter and Veraguth, *Ber.*, 1907, 40, 1432 [2] K Auwers, *Ber.*, 1907, 40, 2154, *Ann.*, 1908, 360, 11

The parent nitrophenols, therefore, which are only known in one form, are to be classed as tautomeric

The true nitrophenolic ethers have been known for a considerable time and are prepared by the usual methods of alkylation The *aci*-ethers are obtained by alkylating the nitrophenol in the form of its silver salt under certain carefully chosen conditions, the true nitrophenolic ether being also produced at the same time

$$C_6H_4\left\langle{}^{NO_2}_{O}\right\rbrace Ag + CH_3I = AgI + \begin{cases} CH_3O\ C_6H_4\ NO_2 \\ O\ C_6H_4\ NO\ OCH_3 \end{cases}$$

The *aci* ethers are intensely red in colour and are formulated as quinonoid compounds, in distinction to the colourless ethers of phenolic structure *Aci*-ethers have much lower melting-points than their isomerides, and without exception are very unstable Even at low temperatures, and when dissolved in indifferent solvents, they isomerise spontaneously with more or less speed into the true ethers Further, they are very easily hydrolysed to nitrophenols, while the genuine nitrophenolic ethers only hydrolyse slowly

According to Hantzsch, it is possible to determine the condition or constitution of the parent nitrophenols directly from their colour [1] Many nitrophenols, such as *p*-nitrophenol and 2 4-dinitrophenol, are colourless (or only faintly yellow), in the solid state such substances are consequently entirely (or almost entirely) true nitro-compounds Others, such as the *o*-nitrophenols, are a little more strongly coloured, although never so intensely so as their esters These are assumed to be solid solutions of a small amount of the coloured *aci*-nitrophenol in a large proportion of the true nitro-compound

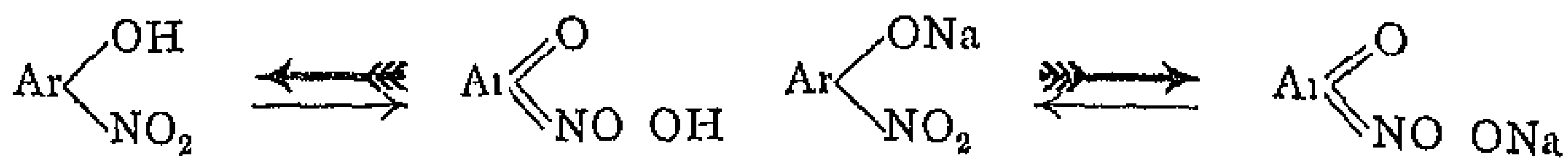
$$C_6H_4\left\langle{}^{OH}_{NO_2}\right. \rightleftarrows C_6H_4\left\langle\!\!\langle{}^{O}_{NO\ OH}\right.$$

Thus ordinary yellow picric acid is supposed to be a solid solution of a little of the coloured quinonoid *aci* trinitrophenol in much of the colourless trinitrophenol [2]

The salts of the nitrophenols with alkalis and alkaline earths are always much more highly coloured than the parent compounds, this indicates that the strongly acidic *aci*-form, barely traceable in the free substance, has been (almost) completely regenerated in the presence of the positive metallic atom, which always tends to attach itself to the most negative part of the molecule. Hence the equilibrium in the case of the free compounds is displaced almost completely in the direction

[1] A Hantzsch, *Ber*, 1906, 39, 1086 [2] *Cf* also Georgievics, *Ber*, 1906, 39, 1536

of the phenolic form, and in the alkali salts equally completely towards the quinonoid form



X

Aromatic Alcohols, Aldehydes and Ketones

When a hydroxyl group is introduced into the side chain of an alkyl benzene, an aromatic alcohol is formed such as benzyl alcohol, $C_6H_5 \cdot CH_2OH$. Compounds of this type may also be regarded as phenyl derivatives of the aliphatic alcohols, which they resemble in most respects. Like the fatty alcohols they may be obtained by heating the corresponding chloro-derivatives with water, by the reduction of aldehydes and ketones, by the action of nitrous acid on amines, and from organo-magnesium halides by combination with aldehydes, ketones or esters. The secondary and tertiary alcohols formed by this last method frequently pass by loss of water into benzene derivatives of olefines (see p. 372).

If we have at our disposal an alcohol, $X \cdot OH$, or the corresponding halogen compound, $X \cdot Cl$, there are three general methods available for synthesising homologues of the formula $X \cdot CH_2OH$ or $X \cdot CH_2Cl$ respectively, viz., 1. Interaction of the halogen compound with potassium cyanide, hydrolysis of the nitrile $X \cdot CN$ to the acid $X \cdot COOH$, esterification to $X \cdot COOC_2H_5$ and reduction of the latter to the alcohol $X \cdot CH_2OH$ (Bouveault). 2. Conversion of $X \cdot Cl$ into $X \cdot MgCl$, which with trioxymethylene yields the alcohol $X \cdot CH_2OH$ (Grignard). 3. By forming the nitrile $X \cdot CN$, reducing it to the amine $X \cdot CH_2 \cdot NH_2$, and allowing the benzoyl derivative of the latter to interact with phosphorus chloride to give $X \cdot CH_2 \cdot Cl$—a method which has been much used recently by J. v. Braun.[1]

Another useful means of preparing alcohols of this type is to shake the corresponding aldehyde with strong aqueous alkali (Cannizzaro reaction).

$$2Cl \cdot C_6H_4 \cdot CHO + KOH = Cl \cdot C_6H_4 \cdot CH_2OH + Cl \cdot C_6H_4 \cdot COOK$$

Benzyl alcohol, *phenyl carbinol*, $C_6H_5 \cdot CH_2OH$, occurs in the free state and in the form of esters in many ethereal oils. It is generally prepared from benzyl chloride by heating with alcoholic potassium acetate, and hydrolysing the benzyl acetate so obtained. It is a colourless liquid of faintly aromatic odour, boiling at 206°, and very

[1] J. v. Braun, Deutsch and Kruber, *Ber.*, 1911, 44, 2867.

sparingly soluble in water. With oxidising agents it yields benzaldehyde and finally benzoic acid. It forms ethers and esters, and on heating with hydrochloric or hydrobromic acid exchanges the hydroxyl group for chlorine or bromine.

Phenyl ethyl alcohol, $C_6H_5.CH_2.CH_2.OH$, b.p. 219°, is the chief constituent of natural and synthetic rose perfume.

Cinnamyl alcohol, *styrone*, or *γ-phenyl allyl alcohol*, is found as the cinnamic ester in *Storax*, and in the juice of the bark of *Liquidambar orientalis*. It is a crystalline compound, m.p. 33° and b.p. 250°, which smells of hyacinths. On gentle oxidation it yields cinnamic acid, and on vigorous oxidation benzoic acid.

Salicyl alcohol, *o-hydroxybenzyl alcohol*, *saligenin*, $HO.C_6H_4.CH_2OH$, is both an alcohol and a phenol, and is formed by the action of enzymes on *salicin*, a glucoside occurring in willow bark, $C_{13}H_{18}O_7 + H_2O = C_6H_{12}O_6 + C_7H_8O_2$. It crystallises in plates melting at 82°.

Aldehydes

The aromatic aldehydes resemble those of the fatty series in reactivity as well as in method of preparation. They may be obtained:

1. By oxidation of the corresponding primary alcohols.
2. From certain dichloro-compounds by heating with water, *e.g.*

$$C_6H_5.CHCl_2 + H_2O = C_6H_5.CH{:}O + 2HCl$$

3. From alkyl derivatives of aromatic hydrocarbons by oxidation with chromyl chloride (*Etard's* reaction).

4. By reducing acid chlorides with hydrogen in the presence of palladised barium sulphate as catalyst.[1] This is a useful practical method. Also by distilling the calcium salts of aromatic carboxylic acids with calcium formate, and by treating iminochlorides in ethereal solution with stannous chloride.[2]

5. Indirectly by the *Friedel-Crafts* reaction, using carbon monoxide, hydrochloric acid gas and an aromatic hydrocarbon, in the presence of aluminium chloride (or aluminium bromide and cuprous chloride). Formyl chloride is formed as an intermediate product.[3]

$$R.C_6H_5 + Cl.C\left\langle\begin{matrix}O\\H\end{matrix}\right. = R.C_6H_4.C\left\langle\begin{matrix}O\\H\end{matrix}\right. + HCl.$$

6. Similarly by using HCN the aldehyde group may be introduced into phenols, phenolic ethers, or their derivatives.[4] The method consists in treating the phenolic compound with HCN and HCl, in some cases with the addition of condensing agents such as aluminium chloride or zinc chloride. Hydrogen cyanide first unites with hydrogen

[1] K. W. Rosenmund, *Ber.*, 1918, 51, 585; 1923, 56, 1481. [2] Sonn and Müller, *Ber.*, 1919, 52, 1927. [3] Gattermann, *Ann.*, 1906, 347, 347. H. Wolf, *Ber.*, 1928, 61, 1765. [4] Gattermann, *Ann.*, 1907, 357, 313. For a simplification of this process, using zinc cyanide in place of hydrogen cyanide, see R. Adams and J. Levine, *J.A.C.S.*, 1923, 45, 2373; 46, 1518.

chloride to form the chloride of iminoformic acid, which then reacts with the phenol, with elimination of hydrochloric acid, to give an aldoimine. The latter, on heating with dilute acids, is readily converted into the aldehyde itself:

$$C_6H_4\begin{matrix} \diagup OCH_3 \\ \diagdown H \end{matrix} \xrightarrow{Cl.CH:NH} C_6H_4\begin{matrix} \diagup OCH_3 \\ \diagdown CH:NH \end{matrix} \xrightarrow{H_2O} C_6H_4\begin{matrix} \diagup OCH_3 \\ \diagdown CH:O \end{matrix}$$

7. Aldehydes are also produced from aromatic organomagnesium compounds by treating these with formic or orthoformic esters,[1] e.g.:

$$CH_3.C_6H_4.MgBr + H.COOC_2H_5 = Br.Mg.OC_2H_5 + CH_3.C_6H_4.CHO$$

Properties.—The aromatic aldehydes are usually pleasant smelling liquids, which in their reducing properties and behaviour towards phenyl-hydrazine, hydroxylamine, and sodium bisulphite resemble the aliphatic aldehydes. They differ from the latter in certain points. For example, they do not polymerise, and on treatment with ammonia they do not yield additive compounds of the type of aldehyde ammonia (see benzaldehyde).

With alkali hydroxides they are converted into a mixture of an alcohol and the salt of a carboxylic acid (*Cannizzaro*), e.g.:

$$2C_6H_5.CHO + KOH = C_6H_5.CH_2OH + C_6H_5.CO_2K$$

Under the influence of potassium cyanide they undergo a peculiar reaction (see benzoin condensation, p. 513). They also combine readily with various aldehydes, ketones, and mono- and dicarboxylic acids with the elimination of water, e.g.:

$$\underset{\text{Benzaldehyde}}{C_6H_5.CHO} + \underset{\text{Acetaldehyde}}{H_3C.CHO} = \underset{\text{Cinnamic aldehyde}}{C_6H_5.CH:CH.CHO} + H_2O$$

With dimethylaniline and with phenols the aromatic aldehydes condense to form triphenyl methane derivatives (see p. 494).

Benzaldehyde, *oil of bitter almonds*, $C_6H_5.CHO$, is formed from the glucoside *amygdalin* occurring in bitter almonds. When the glucoside is treated with the enzyme emulsin, or boiled with dilute acids, it decomposes into benzaldehyde, glucose and hydrogen cyanide:

$$C_{20}H_{27}NO_{11} + 2H_2O = C_6H_5.CHO + 2C_6H_{12}O_6 + HCN$$

Benzaldehyde is employed in industry in the manufacture of dyes and perfumes, for which purpose it is generally prepared from benzal chloride (obtained from toluene) by heating with milk of lime. The product so prepared always contains admixed chloro-derivatives, and may thus be distinguished from natural oil of bitter almonds. It is a colourless liquid of characteristic smell, b.p. 179° and sp. gr. 1.050 at 15°. It is soluble in about 30 parts of water and mixes in all proportions with alcohol and ether. Benzaldehyde readily takes up

[1] Gattermann and Maffezzoli, *Ber.*, 1903, **36**, 4152; *Ann.*, 1906, **347**, 348.

oxygen, even on standing in air, to form benzoic acid. It unites with ammonia to give *hydrobenzamide*,

$$3C_6H_5\cdot CHO + 2H_3N = (C_6H_5CH)_3N_2 + 3H_2O$$

and with aniline to give *benzylidene-aniline*. Compounds of the latter type are known as **Schiff's bases** or **anils**.

$$C_6H_5\cdot CHO + H_2N\cdot C_6H_5 = C_6H_5\cdot CH : N\cdot C_6H_5 + H_2O$$

Under the influence of alcoholic potassium cyanide it condenses to *benzoin*, a ketonic alcohol (see p. 513). When reduced with

$$C_6H_5\cdot CH : O + H\cdot CO\cdot C_6H_5 = C_6H_5\cdot CHOH\cdot CO\cdot C_6H_5 \text{ (Benzoin)}$$

sodium amalgam the latter yields the dihydric alcohol *hydrobenzoin*, $C_6H_5\cdot CHOH\cdot CHOH\cdot C_6H_5$. The **oxime of benzaldehyde**, $C_6H_5\cdot CH : NOH$, exists in two stereoisomeric forms (see also p. 57).

Stereoisomerism of the Aldoximes

According to the relative positions of the hydroxyl group and the hydrogen atom, the aldoximes are distinguished as syn- and anti-aldoximes.

$$\begin{array}{ccc} \begin{array}{r} R\text{—}C\text{—}H \\ \| \quad \\ HO\text{—}N \quad \end{array} & \begin{array}{l} R\text{—}C\text{—}H \\ \quad \| \\ \quad N\text{—}OH \end{array} & \begin{array}{r} R\text{—}C \\ \equiv \\ N \end{array} \\ \text{Anti-aldoxime} & \text{Syn-aldoxime} & \text{Nitrile} \end{array}$$

It has already been mentioned in the general section of this book that aldoximes may lose water and pass into nitriles. Use is made of this reaction for determining their configuration, since the ease with which it is effected differs greatly with the stereoisomeric forms. Hantzsch assumed that it would proceed more readily when the H and OH groups are in adjacent positions, as in the syn-aldoximes, and with difficulty or not at all with the anti-aldoximes. This distinction between the isomerides becomes even more marked in the case of the acetates, $R\cdot CH : N\cdot O\cdot CO\cdot CH_3$. The acetyl derivatives of syn-aldoximes are decomposed quantitatively into acetic acid and a nitrile when warmed with sodium carbonate solution, whereas the anti derivatives remain unattacked.

Aliphatic aldoximes are in general only stable in the syn-form, and their anti-forms can rarely be isolated. Aromatic aldehydes yield anti-aldoximes when treated with hydroxylamine, and these may frequently be transformed into the syn-compounds by means of hydrogen chloride.

Thus benzaldehyde gives *benzantialdoxime*, m.p. 35°, which with hydrochloric acid, sulphuric acid or bromine is converted into *benzsynaldoxime*, m.p. 125°. When the latter is heated the reverse change occurs. As already indicated on pp. 59 and 60 it may be found necessary to reverse the accepted configurations and to assume that the anti-form yields the nitrile more readily than the syn-compound.

p-*Isopropyl benzaldehyde, cuminol*, $(CH_3)_2CH \cdot C_6H_4 \cdot CHO$, is the odorous constituent of oil of cumin. It is a colourless liquid of boiling point 235°, which yields cymene when distilled with zinc dust.

Among **nitro- and amino-derivatives of benzaldehyde** the *o*-compounds are of importance, and are used in the preparation of various heterocyclic substances.

o-**Nitrobenzaldehyde**, $NO_2 \cdot C_6H_4 \cdot CHO$, is formed in about 20 per cent yield by the nitration of benzaldehyde. It is best obtained by the oxidation of *o*-nitrocinnamic acid, or by oxidising *o*-nitrobenzylaniline and hydrolysing the *o*-nitrobenzylidene aniline so obtained. It forms colourless needles, m.p. 46°. In sunlight it readily isomerises into *o*-*nitrosobenzoic acid*, $ON \cdot C_6H_4 \cdot COOH$. Its most important reaction is its conversion into indigo. In the presence of caustic soda it combines with acetone to give $NO_2 \cdot C_6H_4 \cdot CHOH \cdot CH_2 \cdot CO \cdot CH_3$, which immediately parts with acetic acid to form *indigo blue*. *m*-**Nitrobenzaldehyde**, m.p. 58°, is the chief product of the direct nitration of benzaldehyde. *p*-**Nitrobenzaldehyde** is obtained by boiling *p*-nitrobenzyl chloride with lead nitrate solution, and forms colourless prisms, m.p. 107°.

On reduction the above nitrobenzaldehydes are converted into the corresponding amino compounds, $NH_2 \cdot C_6H_4 \cdot CHO$, of which the *m*- and *p*-derivatives are used in the preparation of dye stuffs. *o*-**Aminobenzaldehyde**, m.p. 39°, is distinguished by the ease with which it unites with substances containing the group $-CH_2 \cdot CO-$, when water is eliminated and a derivative of quinoline formed, *e.g.*

$$C_6H_4\begin{cases}NH_2\\CH:O\end{cases} \xrightarrow{CH_3 \cdot CH:O} C_6H_4\begin{cases}NH_2\\CH:CH \cdot CH:O\end{cases} \xrightarrow{-H_2O} C_6H_4\begin{cases}N=CH\\CH=CH\end{cases} \quad \text{Quinoline}$$

Hydroxy or Phenolic Aldehydes

The hydroxy-aldehydes, a number of which occur in nature, can be prepared by two methods.

1. When a phenol in alkaline solution is treated with chloroform, an aldehyde group is introduced into the *o*- or *p*-position to the phenolic hydroxyl[1] (*Reimer-Tiemann* reaction).

$$C_6H_5 \cdot OH + CHCl_3 + 4KOH = KO \cdot C_6H_4 \cdot CHO + 3KCl + 3H_2O$$

2. In the presence of hydrogen chloride phenols react with hydrocyanic acid to form *aldo-imines*, which on boiling with dilute acids are readily converted into the corresponding hydroxy-aldehydes.[2]

$$C_6H_5 \cdot OH \longrightarrow C_6H_4\begin{cases}OH\\CH:NH\end{cases} \longrightarrow C_6H_4\begin{cases}OH\\CH:O\end{cases}$$

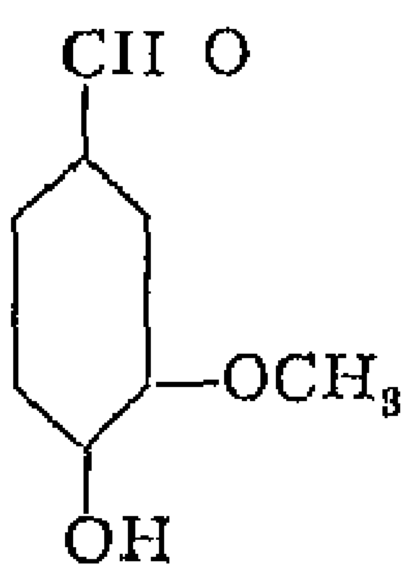
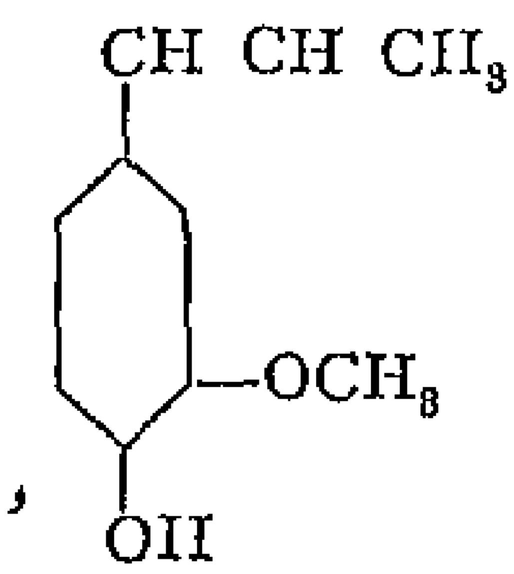
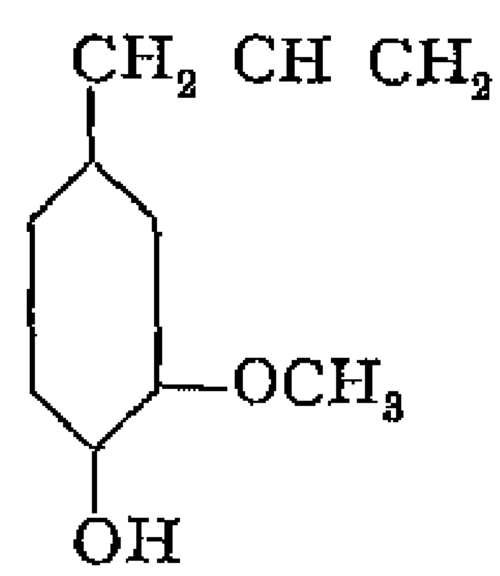
Phenolic aldehydes possess the properties of both phenols and aldehydes.

Salicylaldehyde, *o*-*hydroxy benzaldehyde*, $HO \cdot C_6H_4 \cdot CHO$, is found in the volatile oil of *Spiræa ulmaria*, and is prepared by oxidation of the corresponding alcohol saligenin, or together with *p*-hydroxy benzaldehyde by the action of chloroform on an alkaline solution of phenol. It is a liquid, b.p. 196°, with a smell resembling that of benzaldehyde. On oxidation it yields salicylic acid, and like all *o*-hydroxyaldehydes colours the skin deep yellow.

[1] Reimer, *Ber.*, 1876, **9**, 1268. See also Auwers and Keil, *Ber.*, 1903, **36**, 1861.
[2] Gattermann, *Ber.*, 1898, **31**, 1149, 1765; *Ann.*, 1906, **357**, 347.

Anisaldehyde, p-*methoxy benzaldehyde*, $CH_3O\cdot C_6H_4\cdot CHO$, is formed by the oxidation of anethole, $CH_3O\cdot C_6H_4\cdot CH:CH\cdot CH_3$ (occurring in oil of aniseed, fennel oil and oil of tarragon). It is a colourless liquid, b p 248°, which has an aromatic smell.

Vanillin, m-*methoxy*-p-*hydroxy benzaldehyde* (I), is the active constituent of the vanilla pod, in which it is present to the extent of about 2 per cent. It is the methyl ether of protocatechuic aldehyde, $C_6H_3(OH)_2\cdot CHO$. On the industrial scale vanillin is prepared from the acetyl derivative of *isoeugenol* (II) by oxidising it with chromic acid to give acetyl vanillin, and subsequently removing the acetyl group from the latter. Isoeugenol is obtained from *eugenol* (III), the chief constituent of clove oil, by boiling with alcoholic potash.

I  II  III 

Vanillin may also be prepared synthetically by the above general methods. It crystallises in colourless needles, m p 80°.

Piperonal, *methylene ether of protocatechuic aldehyde, heliotropin*,

$$C_6H_3\begin{cases}[1]\ CHO \\ [3]\ O \\ [4]\ O\end{cases}\!\!>CH_2,$$

is formed when protocatechuic aldehyde is treated with alkali and methylene iodide, and is prepared from isosafrol by cautious oxidation with potassium bichromate and sulphuric acid. It possesses a very pleasant smell resembling that of heliotrope, and is placed on the market as a perfume under the name of heliotropin.

Cinnamic aldehyde, $C_6H_5\cdot CH:CH\cdot CHO$, is an example of an unsaturated aldehyde. It is found in oil of cinnamon and oil of cassia, to which it imparts the odour of cinnamon. From these sources it may be isolated by means of the sodium bisulphite compound. Synthetically it is obtained by the condensation of benzaldehyde with acetaldehyde (see Cinnamic Acid). It is an oil which boils at 246°.

Ketones

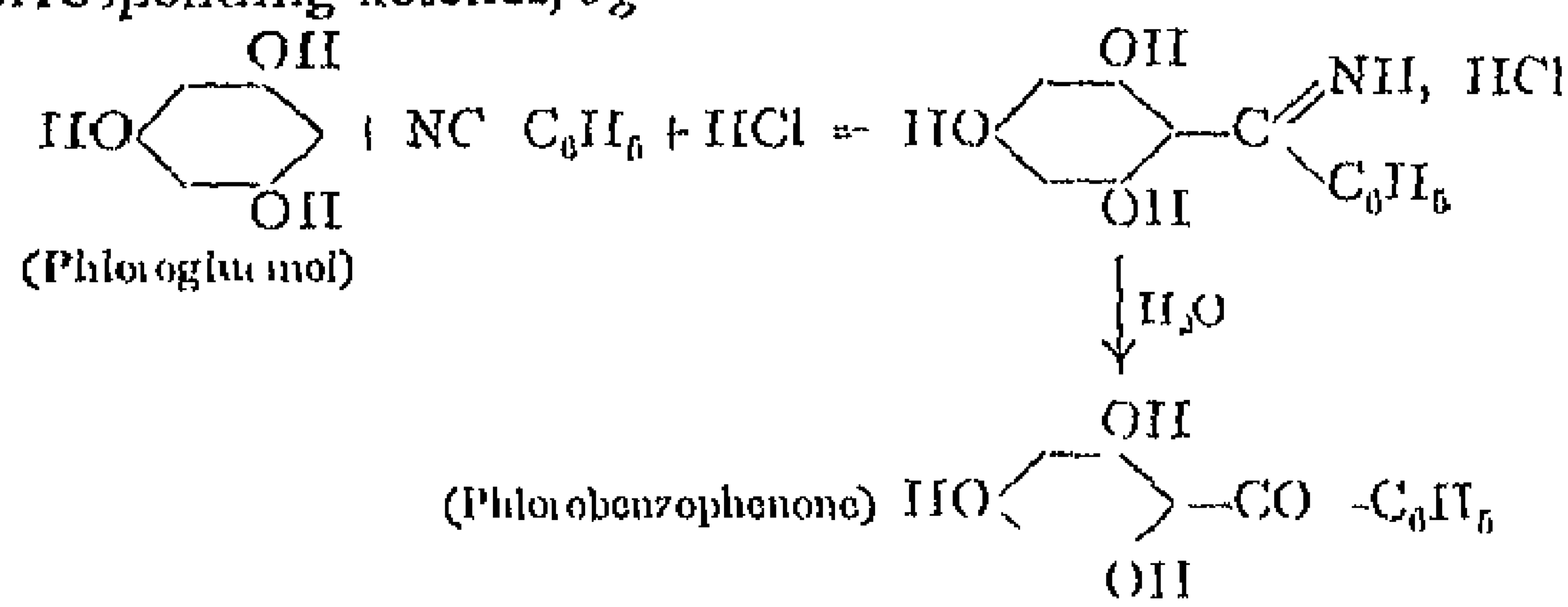
If two aromatic radicals are linked together by a CO— group the resulting compound is a purely aromatic ketone, such as benzophenone, $C_6H_5\cdot CO\cdot C_6H_5$. Ketones containing one aliphatic and one aromatic group attached to the carbonyl group are termed mixed or fatty-aromatic ketones.

Ketones of this type may be regarded as oxidation products of

secondary aromatic alcohols They are formed by the general methods available for ketones (p 167), and also by the Friedel-Crafts reaction from acid chlorides and benzene in the presence of aluminium chloride

$$\underset{\text{Benzene}}{C_6H_6} + \underset{\text{Acetyl chloride}}{CH_3 \cdot CO \cdot Cl} = \underset{\text{Acetophenone}}{C_6H_5 \cdot CO \cdot CH_3} + HCl$$

Aromatic hydroxy ketones may be prepared by the method of *Houben* and *Hoesch*[1] from polyhydric phenols The latter, especially those containing hydroxyl groups in the *m*-position to one another, readily react with aliphatic or aromatic nitriles in the presence of hydrogen chloride to form ketiminochlorides, which on boiling with water yield the corresponding ketones, *e g*



This reaction may be regarded as an extension of *Gattermann's* aldehyde synthesis (p 432)

Aromatic ketones undergo the same typical reactions as those of the fatty series, but, in agreement with the "steric hindrance" observed by V Meyer in connection with the esterification of acids, it is found that no oximes or hydrazones are formed by *o*-disubstituted aromatic ketones[2] of the formula $(CH_3)_2C_6H_3—CO—R$ (in which R is an alkyl radical)

Acetophenone, *phenyl methyl ketone*, $C_6H_5 \cdot CO \cdot CH_3$, is prepared by distilling an equimolecular mixture of calcium acetate and calcium benzoate, or by the interaction of acetyl chloride and benzene in the presence of aluminium chloride It crystallises in large plates, m p 20°, b p. 202°, and is used as a hypnotic under the name of *hypnone*

Benzophenone, *diphenyl ketone*, $C_6H_5 \cdot CO \cdot C_6H_5$, b p 307°, may be obtained by the usual methods and is best prepared by the Friedel Crafts reaction It exists in two modifications, a stable form, m p 49° and a labile form, m p 27°. The latter readily changes into the former Benzophenone on reduction yields the secondary alcohol **benzhydrol,** $C_6H_5 \cdot CHOH \cdot C_6H_5$, m p 68°, and finally *diphenylmethane*, $C_6H_5 \cdot CH_2 \cdot C_6H_5$ (see p 490) When fused with potash it decomposes into benzene and benzoic acid,

$$C_6H_5 \cdot CO \cdot C_6H_5 + KOH = C_6H_5 \cdot COOK + C_6H_6$$

[1] K Hoesch, *Ber*, 1927, 60, 389, 2537; J Houben, *Ber*, 1928, 61, 1597 [2] Baum, *Ber*, 1895, 28, 3207 V Meyer, *Ber*, 1896, 29, 830, 2564

In its other chemical properties, *e g* in its behaviour towards hydroxylamine, phenyl hydrazine and phosphorus pentachloride, it completely resembles the aliphatic ketones When treated in alcoholic solution with dry hydrogen chloride and carbon disulphide, benzophenone yields **thiobenzophenone**,[1] $(C_6H_5)_2CS$, a deep violet crystalline compound, m p 51° to 52°

p-**Diamino-benzophenone**, $CO(C_6H_4 \cdot NH_2)_2$, m p 237°, is formed when fuchsin is boiled with hydrochloric acid

p **Tetramethyl-diamino-benzophenone**, *Michler's Ketone*, is prepared by the action of carbonyl chloride on dimethylaniline

$$2C_6H_5 \cdot N(CH_3)_2 + COCl_2 = CO[C_6H_4N(CH_3)_2]_2 + 2HCl$$

By further condensation with dimethylaniline it yields *Crystal Violet*, and with phenyl-α-naphthylamine it gives *Victoria Blue* (a wool dye) On reduction it passes into the corresponding alcohol *p* **tetramethyl-diamino benzhydrol**, $CHOH[C_6H_4N(CH_3)_2]_2$, which is also employed in the preparation of dye-stuffs

Ketenes — The ketenes (see p 179) are compounds of the general formula $R_2C:CO$ **Diphenyl-ketene**, $(C_6H_5)_2C:CO$, the first member of the group to be prepared, was obtained by Staudinger[2] from diphenyl-chloroacetyl chloride, $(C_6H_5)_2CCl \cdot COCl$, by the removal of chlorine with zinc Diphenyl-ketene is a highly coloured and strongly unsaturated substance It is very reactive and undergoes oxidation in air

XI

Aromatic Carboxylic Acids

Aromatic acids are found free and in the combined state in many resins and balsams They may be prepared by methods similar to those used for aliphatic acids, and by a number of special reactions, of which the following are the most important

1 By oxidation of aromatic hydrocarbons and other benzene derivatives containing side chains, when the latter are converted into carboxyl groups

$$\underset{\text{Toluene}}{C_6H_5 \cdot CH_3} + 3O \rightarrow \underset{\text{Benzoic acid}}{C_6H_5 \cdot COOH} + H_2O$$

A compound with one side chain attached to the nucleus oxidises to a monocarboxylic acid, while the presence of two or three side chains leads to the formation of di- or tricarboxylic acids respectively

2 From salts of sulphonic acids by fusion with sodium formate

[1] H Staudinger und Freudenberger, *Ber*, 1928, 61, 1577, 1837 [2] Staudinger, *Ber*, 1905, 38, 1735, 1906, 39, 968 *Ann*, 1907, 356, 51 *Ber*, 1908, 41, 1355, 1493, 1911, 44, 533, 1913, 46, 1437 G Schroeter, *Ber*, 1909, 42, 2346

3. In a similar manner to aliphatic acids by the hydrolysis of nitriles. The latter are most conveniently prepared from diazonium salts (see p. 395), or by the interaction of benzene-sulphonates with potassium cyanide.

4. Acid chlorides can be prepared by the action of phosgene or oxalyl chloride[1] on benzene and its derivatives in the presence of aluminium chloride (Friedel-Crafts):

$$C_6H_6 + ClCOCl = \underset{\text{Benzoyl chloride}}{C_6H_5 \cdot COCl} + HCl$$

5. Dry carbon dioxide reacts with a mixture of sodium, mercury (or zinc) diethyl, and benzene to form benzoic acid.[2] Homologues of benzene behave similarly, *e.g.* *o*-xylene yields *o*-tolyl-acetic acid.

Aromatic carboxylic acids are usually solid crystalline compounds which are sparingly soluble in water. Like the fatty acids they form chlorides, amides, esters and other derivatives. Further, by substitution in the benzene ring there may be obtained nitro-, amino-, chloro- and other derivatives which are dealt with in more detail later.

I.—MONOBASIC ACIDS

1. Benzoic Acid and its Homologues

Benzoic Acid, $C_6H_5 \cdot COOH$, is found in gum benzoin, in Peru and Tolu balsams, and is present in the form of hippuric acid in the urine of horses. Originally it was prepared by heating gum benzoin, when the acid sublimes, or from hippuric acid, which on boiling with mineral acids is hydrolysed to glycine and benzoic acid. It is still obtained from gum benzoin for pharmaceutical purposes ("acidum benzoicum ex resina"), but otherwise is prepared almost exclusively from toluene. The latter is first converted into benzo-trichloride by treatment with chlorine at the boiling-point, and this is hydrolysed with milk of lime to give calcium benzoate, from which benzoic acid is precipitated by the addition of hydrochloric acid and purified by recrystallisation from water:

$$C_6H_5 \cdot CH_3 \xrightarrow{Cl} C_6H_5 \cdot CCl_3 \xrightarrow{Ca(OH)_2} (C_6H_5COO)_2Ca \xrightarrow{HCl} C_6H_5 \cdot COOH$$

A comparatively small amount of benzoic acid is also prepared by hydrolysis of the benzonitrile present in the middle oil from coal tar, $C_6H_5 \cdot CN \longrightarrow C_6H_5 \cdot COOH$.

Benzoic acid crystallises in colourless, glistening plates and has a faint aromatic smell. It melts at 121°, boils at 250°, very readily sublimes and is volatile in steam. Although only sparingly soluble in cold water, it dissolves readily in the hot liquid, and also in alcohol and ether.

[1] C. Liebermann, *Ber.*, 1911, **44**, 202, 1186. [2] P. Schorigin, *Ber.*, 1908, **41**, 2723; 1910, **43**, 1938.

Salts of the alkali metals are soluble in water, but most of the others are insoluble. When heated with lime, benzoic acid is decomposed into benzene and carbon dioxide. It is employed in medicine and in the manufacture of aniline blue.

Benzoyl chloride, $C_6H_5 \cdot COCl$, is prepared by warming the acid with phosphorus pentachloride or by the action of chlorine on benzaldehyde. It is a colourless liquid, b.p. 199°, with an unpleasant, pungent smell. In behaviour it resembles acetyl chloride, though differing in its greater stability as shown by the slowness with which it is attacked by water. Benzoyl chloride is frequently used as a means of introducing the benzoyl group, $C_6H_5 \cdot CO—$, into hydroxy-, amino- and imino-compounds. This is usually effected by shaking the substance with benzoyl chloride and excess of dilute sodium hydroxide until the smell of the former has disappeared (*Schotten-Baumann reaction*), *e.g.*

$$\underset{\text{Phenol}}{C_6H_5 \cdot OH} + C_6H_5 \cdot CO \cdot Cl = \underset{\text{Phenyl benzoate}}{C_6H_5 \cdot CO \cdot O \cdot C_6H_5} + HCl$$

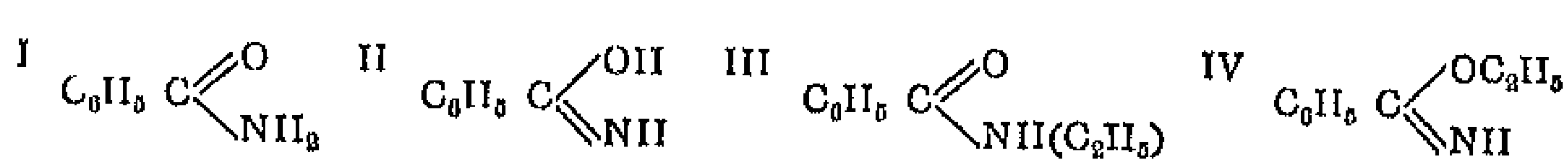
In many cases it is better to use sodium carbonate or pyridine in place of sodium hydroxide.

Benzoyl peroxide, $C_6H_5 \cdot CO \cdot O \cdot O \cdot CO \cdot C_6H_5$, may be obtained in various ways, such as by treating benzoyl chloride in water at 4° with the equivalent amount of sodium peroxide. It is odourless and crystallises in stable white prisms, m.p. 103.5°, which dissolve very sparingly in water, but more readily in alcohol. It is a strong disinfectant and has recently been utilised in this capacity.

Ethyl benzoate, $C_6H_5 \cdot COOC_2H_5$, prepared by the usual methods, is a pleasant-smelling liquid of boiling-point 213°.

For the peculiar behaviour of *o*-substituted benzoic acids on esterification, see p. 364.

Benzamide, $C_6H_5 \cdot CO \cdot NH_2$, is obtained by the action of ammonia or ammonium carbonate on benzoyl chloride. It crystallises in white plates, m.p. 130°, b.p. 288°. When silver benzamide is treated with ethyl iodide it forms the benzimino ether (IV.) instead of the expected ethyl benzamide (III.). Hence benzamide is tautomeric and may react according to either of the formulæ I. or II.



On the other hand, ethyl benzimino ether (IV.) isomerises into ethyl benzamide (III.) on being heated to 100° with ethyl iodide.

Hippuric acid, benzoyl-aminoacetic acid, $C_6H_5 \cdot CO \cdot NH \cdot CH_2 \cdot COOH$ has been mentioned on p. 216. It occurs in the urine of herbivorous animals, and may be prepared from benzamide and chloracetic acid or by the benzoylation of glycocoll. It crystallises in rhombic prisms,

m.p. 187°, and on boiling with alkalis or acids is hydrolysed into benzoic acid and glycocoll.

Benzonitrile, *cyanobenzene*, $C_6H_5 \cdot CN$, is best prepared by heating potassium benzene sulphonate with potassium cyanide. It is an oil, b.p. 191°, with a smell like bitter almonds. In its properties it resembles the fatty nitriles.[1] With sulphuric acid and other condensing agents it polymerises to *cyaphenin*, $C_3N_3(C_6H_5)_3$.

Substituted Benzoic Acids

Chlorine reacts with benzoic acid mainly to form *m-chlorobenzoic acid*, m.p. 153°. The *o*- and *p*-compounds (m.p. 137° and 240°) are obtained from the amino acids by way of the diazonium salts. Chlorine increases the strength of benzoic acid, the effect being greatest in the *o*- and least in the *p*-position.

On nitration benzoic acid yields *m-nitrobenzoic acid*, 141°, the other isomerides also being formed in smaller amounts. The *o*-compound, which is best prepared from *o*-nitrotoluene by oxidation, has a sweet taste and melts at 147°. The *p*-acid from *p*-nitrotoluene melts at 238°.

Among the *aminobenzoic acids*,[2] which possess basic as well as acidic character (see Glycocoll), the most important is the ortho-compound, **anthranilic acid**, m.p. 145°, first obtained by fusing indigo with alkali. It is an important intermediate product in the technical preparation of indigo (described later), for which purpose it is produced in large quantities by the *Hofmann* reaction (p. 160) from phthalimide and chloride of lime or sodium hypochlorite:

$$\underset{\text{Phthalimide}}{C_6H_4\begin{matrix}\diagup CO \diagdown \\ \diagdown CO \diagup\end{matrix}NH} + NaOCl + 3NaOH$$

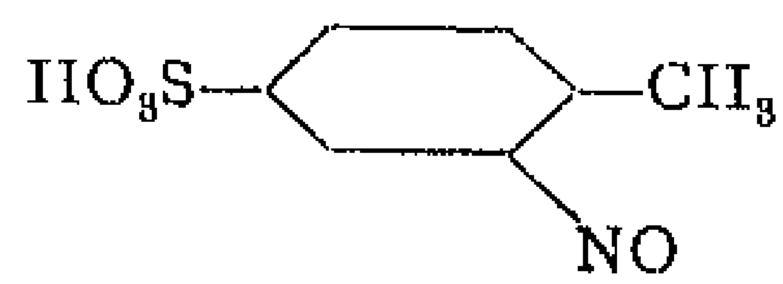
$$= C_6H_4\begin{matrix}\diagup NH_2 \\ \diagdown COONa\end{matrix} + Na_2CO_3 + NaCl + H_2O$$

Other methods have recently been developed for preparing this compound. One of these is based on a peculiar change undergone by *o*-nitrotoluene, which when heated with aqueous or alcoholic sodium hydroxide is directly converted into anthranilic acid:[3]

$$\underset{o\text{-Nitrotoluene}}{C_6H_4\begin{matrix}\diagup NO_2 \\ \diagdown CH_3\end{matrix}} = \underset{\text{Anthranilic acid}}{C_6H_4\begin{matrix}\diagup NH_2 \\ \diagdown COOH\end{matrix}}$$

[1] Many *o*-substituted benzonitriles are difficult to hydrolyse by ordinary reagents, but give excellent yields of acids when heated with anhydrous phosphoric acid, S. C. J. Olivier, *Rec. trav. chim.*, 1929, 48, 568. [2] The Kolbe synthesis of hydroxy benzoic acids from phenoxides and carbon dioxide may be applied to the halogen magnesium compounds of arylamines. By heating these with carbon dioxide, secondary and tertiary aromatic amines can be converted into amino acids. J. Houben and Freund, *Ber.*, 1913, 46, 3833. [3] Preuss and Binz, *Z. ang. Ch.*, 1900, 16, 385.

The intramolecular rearrangement occurs particularly easily in the case of the nitrotoluene sulphonic acid of the formula



This yields the corresponding sulphonated anthranilic acid, from which the sulphonic group is readily removed by electrolytic reduction in neutral or slightly acid solution, with production of anthranilic acid.[1]

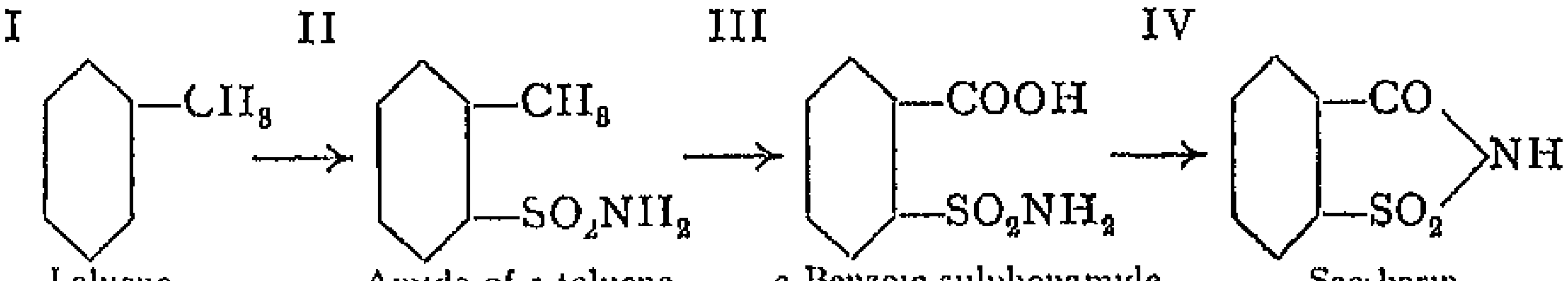
Anthranilic acid and its alkyl- or aryl-substitution products can also be prepared from *o*-chlorobenzoic acid, by treatment with ammonia or amines in the presence of copper powder.

The acid is soluble in water and alcohol, possesses a sweet taste, and on heating readily decomposes into aniline and carbon dioxide.[2] *Methyl anthranilate*, $NH_2 \cdot C_6H_4 \cdot COOCH_3$, m.p. 25°, is contained in the oils of orange blossom and *tuberosa* blossom.

Certain derivatives of the aminobenzoic acids are of physiological interest.[3] It has already been mentioned that all aromatic esters are capable of inducing local anæsthesia, and among the numerous amino-alkyl esters of aromatic amino- and polyamino-acids which have been prepared, one of these, viz., the *diethylamino-ethyl ester* of p-*aminobenzoic acid*, meets the requirements so well that it is used in the form of its hydrochloride, $NH_2 \cdot C_6H_4 \cdot COO \cdot CH_2 \cdot CH_2 \cdot N(C_2H_5)_2,HCl$, as a local anæsthetic in medicine and dentistry under the name of *novocaine*. It crystallises from absolute alcohol in needles, m.p. 156°.

The three sulphobenzoic acids, $SO_3H \cdot C_6H_4 \cdot COOH$, are obtained from the three toluene sulphonic acids by oxidation with potassium permanganate. *m-Sulphobenzoic acid*, accompanied by a little *p*-compound, is the chief product of the sulphonation of benzoic acid. The *imide of* o-*sulphobenzoic acid* (IV.) is 500 times sweeter than sugar, and is sold as a sugar substitute under the name of **saccharin**. It is manufactured from toluene (I.), which by sulphonation gives *o*-toluene-sulphonic acid, the amide of which (II.) yields saccharin on oxidation. The *o*-benzoic-sulphonamide (III.) formed in the last stage immediately loses water.

I II III IV



Toluene. Amide of *o*-toluene sulphonic acid. *o*-Benzoic sulphonamide. Saccharin.

[1] See *J. C. S.*, 1904, A, i, 159.

[2] For *anthranil*, $C_6H_4<\binom{CH}{N}>O$, an inner anhydride of anthranilic acid, see E. Bamberger, *Ber.*, 1904, 37, 966.

[3] A. Einhorn, *Ann.*, 1910, 371, 125.

Saccharin itself is only sparingly soluble in water, but owing to the presence of the imido-group it possesses acidic properties, and forms salts. The sodium salt, $C_6H_4\genfrac{<}{>}{0pt}{}{CO}{SO_2}NNa$, dissolves readily in water and is about 400 times sweeter than sugar.

Homologues of Benzoic Acid and their Derivatives

Homologues of benzoic acid may be of two types, namely alkylated benzoic acids, R . C_6H_4 . COOH, and phenyl-substituted aliphatic acids, C_6H_5 . R . COOH. The former resemble benzoic acid more closely than the latter.

Cumic acid, p-*isopropyl benzoic acid*, C_3H_7 . C_6H_4 . COOH, m.p. 116°, is formed by the oxidation of cymene (p. 372) or of cuminol, and is therefore prepared by oxidising oil of cumin with potassium permanganate.

Phenyl acetic acid, C_6H_5 . CH_2 . COOH, m.p. 76°, is conveniently obtained from benzyl chloride by the Grignard reaction, and is also formed during the putrefaction of proteins.

$$C_6H_5 . CH_2 . Cl \xrightarrow{Mg} C_6H_5CH_2MgCl \xrightarrow{CO_2} C_6H_5 . CH_2 . COOH$$

Mandelic acid, *phenyl-glycollic acid*,[1] C_6H_5 . CHOH . COOH, contains an asymmetric carbon atom, and hence occurs in two optically active forms and an inactive racemic form. The latter, m.p. 118°, may be obtained by the addition of HCN to benzaldehyde, and hydrolysing the cyanhydrin so produced by means of hydrochloric acid. It can be resolved into the active acids (m.p. 133°) by recrystallisation of the cinchonine salts. l-*Mandelic acid*, the naturally occurring form, is prepared by warming amygdalin with fuming hydrochloric acid. On oxidation mandelic acid yields *benzoyl-formic acid*, or *phenyl-glyoxalic acid*, C_6H_5 . CO . COOH, m.p. 66°.

Phenyl propionic acids, $C_6H_5(C_2H_4)COOH$. α-Phenyl propionic acid, or *hydratropic acid*, C_6H_5 . $CH(CH_3)$. COOH, is a liquid, b.p. 265°, obtained by the reduction of atropic acid (see index). β-Phenyl propionic acid or *hydrocinnamic acid*, C_6H_5 . CH_2 . CH_2 . COOH, m.p. 47°, b.p. 280°, is formed by the reduction of cinnamic acid, C_6H_5 . CH : CH . COOH, and is produced during the putrefaction of proteins.

Phenyl-alanine, β-*phenyl-α-amino-propionic acid*, C_6H_5 . CH_2 . $CH(NH_2)$. COOH, m.p. 283° to 284°, occurs with asparagine in the embryo of vetch; the *l*-form is produced by the putrefaction or hydrolysis of proteins such as silk fibroin, oxyhæmoglobin and casein. It may be prepared in the racemic form by reducing α-amino-cinnamic acid with sodium amalgam, or by the action of ammonia on phenyl-

[1] Phenyl amino acetic acid, amino phenyl acetic acid, and phenyl glycine are treated in connection with the indole group. For the configuration of mandelic acid see K. Freudenberg, *Ber.*, 1923, 56, 193.

bromo propionic acid By making use of its benzoyl derivative, the *r*-acid may be resolved into its active components

2 Monobasic Unsaturated Acids

Cinnamic acid, *β-phenyl-acrylic acid*, $C_6H_5 \cdot CH : CH \cdot COOH$, is found free or as an ester in Peru and Tolu balsams and in storax It can be prepared by a variety of methods

1 By *Perkin's* reaction, in which benzaldehyde is condensed with sodium acetate in the presence of acetic anhydride Combination proceeds in two stages, as follows

$$\underset{\text{Benzaldehyde}}{C_6H_5 \cdot CHO} \xrightarrow{+H_3C \cdot COONa} C_6H_5 \cdot CH(OH) \cdot CH_2 \cdot COONa \xrightarrow{-H_2O} \underset{\text{Sodium cinnamate}}{C_6H_5 \cdot CH : CH \cdot COONa}$$

Perkin's reaction may be applied to the synthesis of numerous unsaturated acids and their substituted derivatives In the above example, benzaldehyde may be replaced by its homologues, its halogen- or nitro-substitution products, etc, and the place of sodium acetate may be taken by salts of homologous acids, aryl-substituted acetic acids, halogen-substituted fatty acids or dibasic fatty acids

2 By the *Claisen* condensation, using benzaldehyde and acetic ester in the presence of sodium ethoxide or metallic sodium,

$$C_6H_5 \cdot CHO + H_3C \cdot CO_2C_2H_5 = C_6H_5 \cdot CH : CH \cdot CO_2C_2H_5$$

This reaction is also of general application

3 Technically it is prepared from benzal chloride by heating with sodium acetate

Cinnamic acid, m p 133°, b p 300°, crystallises from hot water in needles It possesses the properties characteristic of ethylene derivatives, adding on bromine and hydrogen, and decolorising alkaline permanganate solution

The cinnamic acids present an unusual case of isomerism As explained on p 49, ethylene derivatives can exist in two isomers of different space arrangement, the theoretical possibilities in the case of cinnamic acid being formulated as

$$\text{I} \quad \begin{array}{c} H-C-C_6H_5 \\ \| \\ H-C-COOH \end{array} \qquad \text{and} \qquad \text{II} \quad \begin{array}{c} C_6H_5-C-H \\ \| \\ H-C-COOH \end{array}$$

In actual fact, however, there are in addition to ordinary cinnamic acid, which is assigned the *trans* configuration II, no less than three *cis*-forms of the configuration I, namely

1 Liebermann's *iso*-cinnamic acid, m p about 57°
2 Erlenmeyer's *iso*-cinnamic acid, m p 38° to 46°
3 Liebermann's *allo*-cinnamic acid,[1] m p 68°

[1] Liebermann, *Ber*, 1892, 25, 950 Stoermer und Heymann, *Ber*, 1912, 45, 3099

The last of these acids has been known for a considerable time, but the existence of the two *iso*-acids has been the subject of much discussion.[1] Liebermann's *iso*- and *allo*-cinnamic acids were first isolated as by-products during the preparation of cocaine. A mixture of these two acids with a small proportion of ordinary cinnamic acid was obtained later by Michael by the reduction of β-bromocinnamic acid (m.p. 159°). Eventually the researches of Biilmann[2] proved the separate existence of all three *cis* acids, and also that, from the chemical point of view, they are not isomeric but identical. We are dealing here with a case of trimorphism, and in a few seconds any one of the three acids can be changed into any other, merely by melting it and seeding out the cooled melt with a crystal of the desired form.

o-**Nitrocinnamic acid**, m.p. 240°, is of interest in connection with the synthesis of indigo. It is formed together with the *p*-compound by treating cinnamic acid with concentrated nitric acid.

When the dibromide of *o*-nitrocinnamic acid is boiled with alcoholic potash it yields *o*-**nitrophenyl-propiolic acid**, $NO_2 \cdot C_6H_4 \cdot C:C \cdot COOH$, which with reducing agents such as glucose and potassium hydroxide, hydrogen sulphide, or ferrous sulphate, is converted into indigo blue.

Atropic acid, *a-phenyl acrylic acid*, $CH_2:C(C_6H_5) \cdot COOH$, m.p. 106°, is obtained from *tropic acid*, $CH_2OH \cdot CH(C_6H_5) \cdot COOH$ (a disruption product of the alkaloids atropine and hyoscyamine), by heating with hydrochloric acid or baryta water.

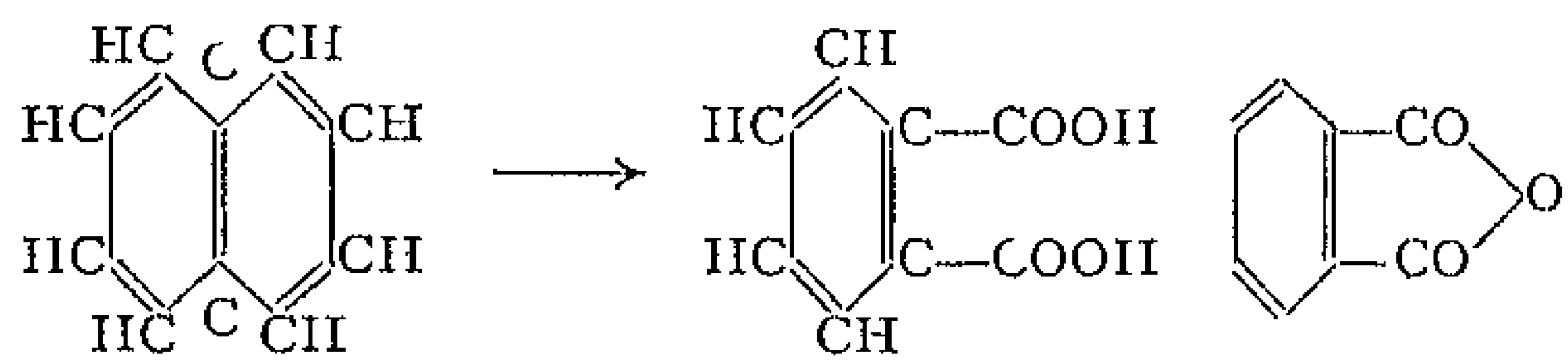
II.—POLYBASIC ACIDS

Polybasic aromatic acids may contain the carboxyl groups entirely in the nucleus, entirely in side chains (aryl-substituted fatty acids), or partly in the nucleus and partly in side chains. Chief among them, from the theoretical as well as the practical standpoint, are the dibasic phthalic acids. Reference is frequently made to these acids in determining the position of side chains in a benzene derivative, and the *o*-acid, ordinary phthalic acid, is also employed in the preparation of various dye-stuffs.

Phthalic acid, *benzene-o-dicarboxylic acid*, $C_6H_4(COOH)_2$, is the final oxidation product of a number of benzene derivatives containing two organic side chains in the ortho-position. It is used in large quantities in the manufacture of indigo and other dyes, for which purpose it is prepared by heating naphthalene with fuming sulphuric acid, with the addition of mercuric sulphate as catalyst. During the

[1] E. Erlenmeyer, jun., *Ber.*, 1905, **38**, 2562, 3496, 3499, 3891; 1906, **39**, 285, 1570; 1909, **42**, 2663. *Cf.* also Marckwald and Meth, *Ber.*, 1906, **39**, 1171. [2] E. Biilmann, *Ber.*, 1909, **42**, 182. C. Liebermann, *Ber.*, 1909, **42**, 1027, 4659. De Jong, *C.*, 1919, **III**, 821. *Ber.*, 1922, **55**, 463. *C.*, 1922, **I**, 1023. *Ber.*, 1923, **56**, 818.

oxidation sulphur trioxide becomes reduced to sulphur dioxide, $SO_3 = SO_2 + O$, which is recovered and converted into the trioxide

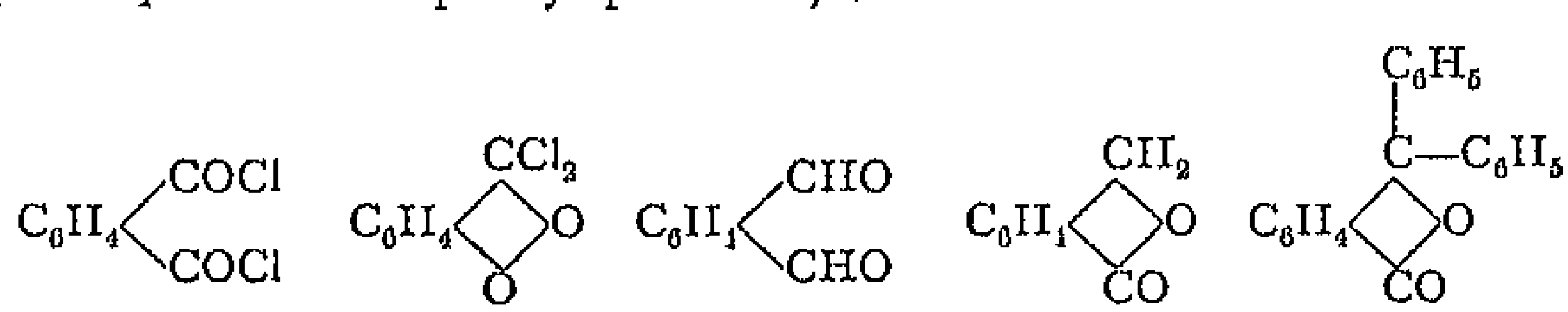


Naphthalene Phthalic acid Phthalic anhydride

By the more recent process of Wohl and Gibbs phthalic acid or its anhydride may be prepared technically in almost quantitative yield by passing naphthalene vapour and air over vanadium pentoxide heated to 450°-520°

Phthalic acid crystallises in glistening plates, which are moderately soluble in hot water When heated it loses water and passes into the anhydride

Phthalic anhydride forms long needles, m p 128°, b p 285° With phosphorus pentachloride it yields *phthalyl chloride* From an examination of its optical refraction and absorption in ultraviolet light[1] phthalyl chloride has been assigned the symmetrical structure, I (see below) When treated with aluminium chloride[2] it is transformed into an isomeric modification, II These two forms exhibit chemical as well as physical differences The symmetrical chloride gives a greenish-yellow solution with guaiacol and acenaphthene, whereas the unsymmetrical form remains colourless[3] In this respect the two isomerides resemble phthalaldehyde, III, and phthalide, IV, the former of which is symmetrical and dissolves in dimethylaniline to give an orange-yellow colour, whilst the latter is unsymmetrical and yields a colourless solution The chlorides also exhibit differences in other reactions With zinc dust and acetic acid both phthalyl chlorides are reduced to phthalide, IV, and with benzene and $AlCl_3$ they form *phthalophenone* or diphenyl-phthalide, V



I II III IV V

Phthalic anhydride condenses with phenols to form triphenyl-methane dye-stuffs, which are known collectively as **phthaleins** The reaction proceeds by the *p*-hydrogen atoms of two molecules of phenol uniting

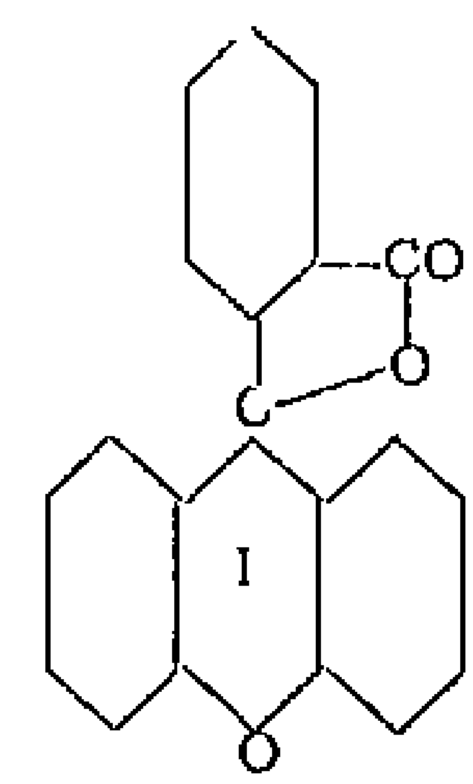
[1] J Scheiber, *Ber*, 1912, 45, 2252 [2] E Ott, *Ann*, 1912, 392, 245 [3] P Pfeiffer, *Ber*, 1922, 55, 413

with a carbonyl oxygen atom of anhydride to give water The simplest of these compounds is *phenol phthalein*, formed as follows —

$$\begin{array}{l} C_6H_4{-}CO \\ |\qquad\quad | \\ CO{-}{-}O \end{array} + \begin{array}{l} H\ C_6H_4\ OH \\ \\ H\ C_6H_4\ OH \end{array} = \begin{array}{l} C_6H_4\ C \begin{cases} \overset{[1]}{C_6H_4}\ \overset{[4]}{OH} \\ C_6H_4\ OH \end{cases} \\ |\qquad | \\ CO{-}O \end{array} + H_2O$$

Phenol phthalein

In the above condensation of phthalic anhydride with phenol the main reaction is accompanied by the formation of fluorane (of the annexed formula), which may be regarded as the parent substance of the fluoresceins and rhodamines (see below) In this case the two phenolic groups have condensed in the ortho instead of the para positions, and by the elimination of an additional molecule of water between the hydroxyl groups an oxygen ring, I (pyrone ring), has been formed



Phthaleins may be considered as substitution products of the above-mentioned phthalophenone, which is the inner anhydride of triphenyl carbinol-*o* carboxylic acid Many of them are of industrial value as dyes

Phenol phthalein (formula, see above) is prepared by heating phthalic anhydride and phenol to 120°, in the presence of concentrated sulphuric acid It forms colourless crystals, which dissolve in alkali to give an intense red solution, from which the compound is precipitated in the colourless state by the addition of acids On this colour-change depends its use as an indicator in volumetric analysis If in the above condensation resorcinol is used in place of phenol, the inner anhydride of resorcinol phthalein, or *fluorescein*, is formed (formula, see below) It is a dark yellow crystalline substance, soluble in alkalis to yellowish-red solutions, which, particularly when dilute, exhibit a magnificent green fluorescence *This characteristic property of fluorescein and similarly constituted phthaleins is used as a test for* meta-*dihydroxybenzene derivatives* (see p 418) *as well as for phthalic anhydride* Fluorescein is the starting-point in the preparation of most of the important dye-stuffs derived from phthalic acid When treated with bromine, substitution occurs in the resorcinol groups with the formation, for example, of *tetrabromo-fluorescein*, $C_{20}H_8O_5Br_4$, the potassium salt of which is used industrially under the name of *eosin* In a weakly acid bath the latter dyes wool and silk fine shades of red

$$\begin{array}{l} C_6H_4\ \overset{[1]}{C} \begin{cases} C_6H_3 \begin{cases} OH[^4] \\ \\ \end{cases} \\ \qquad\quad > O[^2] \\ C_6H_3 \begin{cases} \\ OH[^4] \end{cases} \end{cases} \\ CO{-}O \end{array} \qquad\qquad \begin{array}{l} C_6H_4\ C \begin{cases} C_6HBr_2 \begin{cases} OH \\ \\ \end{cases} \\ \qquad\quad > O \\ C_6HBr_2 \begin{cases} \\ OH \end{cases} \end{cases} \\ CO{-}O \end{array}$$

Fluorescein[1] Eosin

[1] The figures in brackets indicate the position of the substituents in the benzene nucleus

In place of phthalic anhydride its di- and tetrachloro derivatives may also be fused with resorcinol, with the production of fluoresceins which are chlorinated in the phthalic acid group. From these, by bromination and iodination, are prepared the dye stuffs known as *Phloxines* and *Rose Bengals* respectively. The dyes obtained from chlorinated phthalic acids are distinguished from derivatives of ordinary fluorescein by a somewhat bluer shade of red, and are employed particularly in dyeing silk. *Gallein*, prepared by fusing together phthalic anhydride and pyrogallol, is a violet dye, which with concentrated sulphuric acid at 200° yields *Coerulein*. The latter dyes green and is a derivative of phenyl anthracene.

The **Rhodamines** form another group of dyes, and are phthaleins of *m*-aminophenol and its N-alkylated derivatives. They are obtained by condensing phthalic anhydride with *m*-aminophenols, and are among the finest of the red dyes. The rhodamines are regarded as diamino-derivatives of fluorane. Commercial rhodamine consists mainly of the phthalein of diethyl *m*-aminophenol.

$$\begin{matrix} C_6H_4\cdot CO \\ CO-O \end{matrix} + 2HC_6H_3\left\langle\begin{matrix} N(C_2H_5)_2 \\ OH \end{matrix}\right. = \begin{matrix} C_6H_4\cdot C \\ CO-O \end{matrix}\left\langle\begin{matrix} C_6H_3\left\langle\begin{matrix} N(C_2H_5)_2 \\ \end{matrix}\right. \\ O \\ C_6H_3\left\langle\begin{matrix} \\ N(C_2H_5)_2 \end{matrix}\right. \end{matrix}\right. + 2H_2O$$

Phthalic anhydride — Diethyl *m*-aminophenol — Rhodamine[1]

Phthalimide, $C_6H_4\left\langle\begin{matrix} CO \\ CO \end{matrix}\right\rangle NH$, m.p. 238°, can be prepared by the action of ammonia on phthalic anhydride. It is used, on the one hand, for the technical preparation of anthranilic acid, and on the other for the production of primary aliphatic amines and primary amino-acids by Gabriel's method (see p. 211), which has also been modified by E. Fischer for the synthesis of diamino-acids[2] (*cf.* Ornithine). The synthesis of primary amines by this method is effected as follows[3]: Phthalimide reacts with alcoholic potash to form *potassium phthalimide*, $C_6H_4:(CO)_2:NK$, which when treated with alkyl halides exchanges the metallic atom for an alkyl radical. The alkyl phthalimide so obtained may be decomposed by heating with fuming hydrochloric acid, to give phthalic acid and a primary amine.

$$C_6H_4:(CO)_2:NK + IC_2H_5 = C_6H_4:(CO)_2:N\cdot C_2H_5 + KI$$
$$C_6H_4:(CO)_2:N\cdot C_2H_5 + 2H_2O = C_6H_4(COOH)_2 + C_2H_5\cdot NH_2$$

Isophthalic acid, *benzene-m-dicarboxylic acid*, $C_6H_4(COOH)_2$, results from the oxidation of benzene derivatives containing two carbon chains in the *m* position, and may be prepared by oxidising *m*-xylene with calcium permanganate. It

[1] In the rhodamines the NH_2 or $N(Alk)_2$ group occupies the *p* position to the carbon atom of the phthalic residue. [2] E. Fischer, *Ber.*, 1906, 39, 534. [3] For valuable improvements in this method see Ing and Manske, *J. C. S.*, 1926, 129, 2348.

crystallises in fine needles, m p 348°, which are difficultly soluble in water It forms no anhydride A derivative of isophthalic acid has already been mentioned in *uvitic acid* (see p 255)

Terephthalic acid, *benzene p dicarboxylic acid*, $C_6H_4(COOH)_2$, is formed in the same manner from *p* disubstitution products of benzene, *e g* by the oxidation of *p* xylene It is obtained by the oxidation of oil of cumin (cymene + cuminol) is a white amorphous powder, which on being heated sublimes without melting It forms no anhydride

Of the three isomeric *tricarboxylic acids* of benzene the most important is **trimesic acid** (1 3 5) It can be prepared from the corresponding trisulphonic acid, by conversion into the nitrile and subsequent hydrolysis A more interesting synthesis is by polymerisation of the aliphatic compound propiolic acid Trimesic acid sublimes about 200° and melts at 380°

Mellitic acid, *benzene-hexacarboxylic acid*, $C_6(COOH)_6$, is present as its aluminium salt, $C_{12}Al_2O_{12}+18H_2O$, in peat Owing to its yellow colour the salt is known as honey-stone The acid is obtained by oxidising hexamethyl benzene with permanganate, and also by oxidising wood charcoal or graphite with fuming nitric acid It crystallises in fine white needles, decomposes on heating, and when distilled with lime yields benzene

III — PHENOLIC ACIDS

Aromatic hydroxy-acids containing the hydroxyl group in an aliphatic side chain resemble in many ways the hydroxy-acids of the fatty series, and the more important representatives of these aromatic alcohol-acids have already been mentioned On the other hand, aromatic acids in which a hydroxyl group is attached to the nucleus combine the properties of an acid with those of a phenol, and are therefore described as phenolic acids They may be obtained by a number of methods, of which the following are the most important

1 From amino-acids by diazotisation and boiling the resulting diazo compound with water

2 By the fusion of sulphobenzoic acids with alkali hydroxides

3 By the action of carbon dioxide on alkali phenoxides at high temperature (see Salicylic Acid)

4 By the interaction of carbon tetrachloride and phenols in alkaline solution

$$C_6H_5OK + CCl_4 + 4KOH = C_6H_4(OH)CO_2K + 4KCl + 2H_2O$$

The carboxyl group tends to assume the *p*-position to the hydroxy group

5 From benzene homologues or from phenols by fusion with caustic alkali and lead dioxide In this manner *o*-cresol yields salicylic acid

Monohydroxy-monocarboxylic Acids

1. *Hydroxy-benzoic Acids*

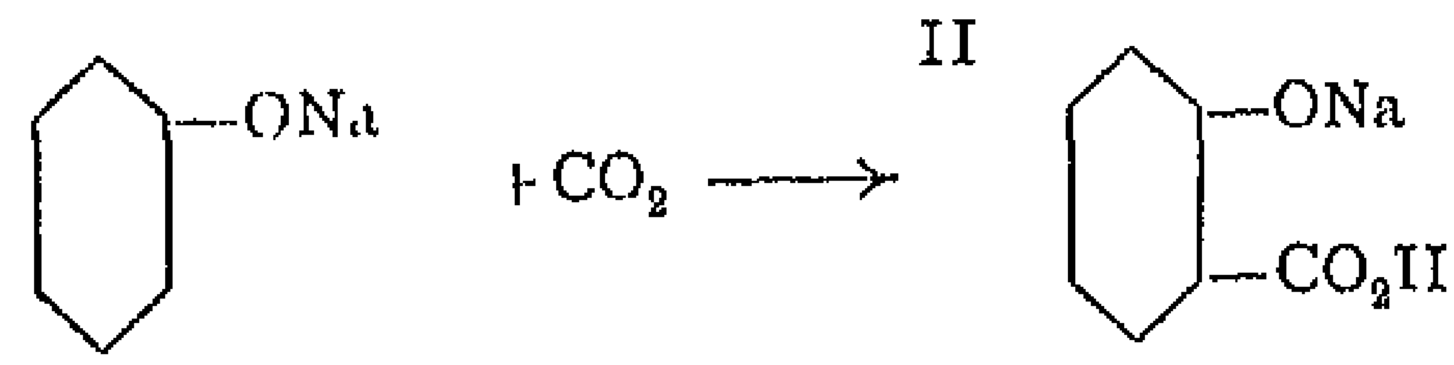
Salicylic acid, *o-hydroxy-benzoic acid*, $C_6H_4\left<\begin{matrix}OH\\COOH\end{matrix}\right.$, occurs in the form of its methyl ester as the chief constituent of oil of wintergreen, from which it is isolated for therapeutic purposes. The corresponding phenolic alcohol, saligenin (see index), is a component of the glucoside salicin. Salicylic acid may be formed by the above general methods, and is prepared technically by heating sodium phenoxide with carbon dioxide under pressure at about 140°.

For a long time this reaction was assumed to take the following course:

$$\underset{\text{Phenol}}{C_6H_5ONa + CO_2} \longrightarrow \underset{\text{Sodium phenyl carbonate}}{C_6H_5O\,C\left<\begin{matrix}O\\ONa\end{matrix}\right.} \longrightarrow \underset{\text{Sodium salicylate}}{C_6H_4\left<\begin{matrix}OH\\CO_2Na\end{matrix}\right.}$$

but as a result of later investigation[1] it appears that the simplest explanation is the correct one, the sodium phenate (I) combining directly with carbon dioxide, at the temperature employed, to form the sodium derivative of phenol-*o*-carboxylic acid (II).

I II



Free salicylic acid is precipitated by the addition of mineral acid and recrystallised from hot water. It forms colourless needles, m.p. 155°, which dissolve sparingly in cold water, and readily in hot water or chloroform. In aqueous or alcoholic solution it gives a violet coloration with ferric chloride. It is employed as an antiseptic, particularly in the preservation of food, and is used in the preparation of dye-stuffs. It was also used medicinally in cases of rheumatism, but it produces certain undesirable after-effects and has now been displaced by derivatives such as *aspirin* (acetyl salicylic acid), $CH_3CO \cdot O \cdot C_6H_4 \cdot COOH$, (m.p. 128°) having a milder action.

When salicylic acid is treated with an equivalent proportion of a phenol in the presence of phosgene or phosphorus oxychloride, esters are obtained. Thus *phenyl salicylate*, usually termed *salol*, $C_6H_4(OH)COOC_6H_5$, is prepared by the action of phosgene on a mixture of phenol and salicylic acid. It melts at 42° and is used as an antiseptic. The β-naphthyl ester of salicylic acid, *betol*, $C_6H_4(OH)COOC_{10}H_7$, serves the same purpose, and the acetyl *p*-

[1] See *Ber.*, 1905, 38, 1375; 1906, 39, 14.

aminophenyl ester, known as *salophene*, is used as a remedy for headache. Many esters of salicylic acid are employed as perfumes.

Meta and para hydroxy benzoic acids, m.p. 200° and 210° respectively, can be prepared from the corresponding amino and halogen substituted benzoic acids. The acids are of little importance but some of their derivatives are of interest. *Methyl p amino m hydroxy benzoate*, m.p. 121°, is used as a local anaesthetic (under the name of *orthoform*), as is also the *m* amino *p* hydroxy derivative (*new orthoform*).

p *Methoxy benzoic acid, anisic acid*, $CH_3O \cdot C_6H_4 \cdot COOH$, is formed by the oxidation of oil of aniseed, and may be prepared from *p* hydroxybenzoic acid by methylation with methyl iodide and alkali, or from *p* bromo-anisole by the Grignard reaction, using magnesium and carbon dioxide. It melts at 185°, and boils at 280°.

2. *Monobasic Phenolic Acids with Carboxyl in the Side Chain, and the Coumarins*

p **Hydroxy phenyl propionic acid**, *hydrocoumaric acid*, $HO \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot COOH$ (see p. 449), results from the putrefaction of tyrosine, and occurs in old cheese and in the pancreas. It is obtained by the hydrolysis of proteins and forms monoclinic crystals, m.p. 128°. The *α* amino derivative of this acid is tyrosine.

Tyrosine, p-*hydroxy-phenyl-alanine*, $HO \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot COOH$, occurs as the *l*-form (m.p. 314 to 318°) in old cheese, the berries of the elder, the spleen, the pancreatic gland and in diseased liver. It is also produced from many proteins by hydrolysis with dilute acids,[1] by pancreatic digestion, or by putrefaction. *r*-Benzoyl tyrosine can be conveniently obtained by the method of Erlenmeyer, jun. *p*-Hydroxybenzaldehyde, $HO \cdot C_6H_4 \cdot CHO$, is condensed with hippuric acid, $H_2C(NH \cdot CO \cdot C_6H_5) \cdot COOH$, to give *p*-hydroxy-*α*-benzoylaminocinnamic acid, $HO \cdot C_6H_4 \cdot CH : C(NH \cdot CO \cdot C_6H_5) \cdot COOH$, which on reduction with sodium amalgam yields *r*-benzoyl-tyrosine, m.p. 192°. By crystallisation of the brucine and cinchonine salts E. Fischer succeeded in resolving this acid into *l*- and *d*-benzoyl-tyrosines (m.p. 162°). From the benzoyl derivatives *l*-, *d*- *and r-tyrosines* can be prepared by heating with hydrochloric acid. A physiologically important derivative of tyrosine is the hormone, *thyroxine* (p. 671).

Tyrosol, or p-*hydroxyphenyl ethyl alcohol*,[2] is produced by the fermentation of tyrosine with sugar and compressed yeast.

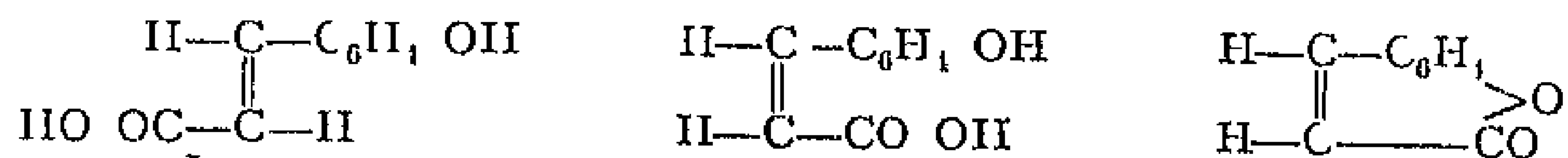
$$\underset{\text{Tyrosine}}{HO \cdot C_6H_4 \cdot CH_2 \cdot CH(NH_2) \cdot CO_2H} \longrightarrow \underset{\text{Tyrosol}}{HO \cdot C_6H_4 \cdot CH_2 \cdot CH_2 \cdot OH}$$

Tyrosol crystallises in small, colourless needles, m.p. 93° and b.p. about 310°. It is a normal product of the protein metabolism of yeast and hence is a by-product of all kinds of yeast fermentations,

[1] See formation of *l* tyrosine from silk fibroin, E. Fischer, *Z. physiol. Ch.*, 1901, **33**, 181.
[2] F. Ehrlich, *Ber.*, 1911, **44**, 139.

being found in the majority of fermented beverages, particularly in beer and wine

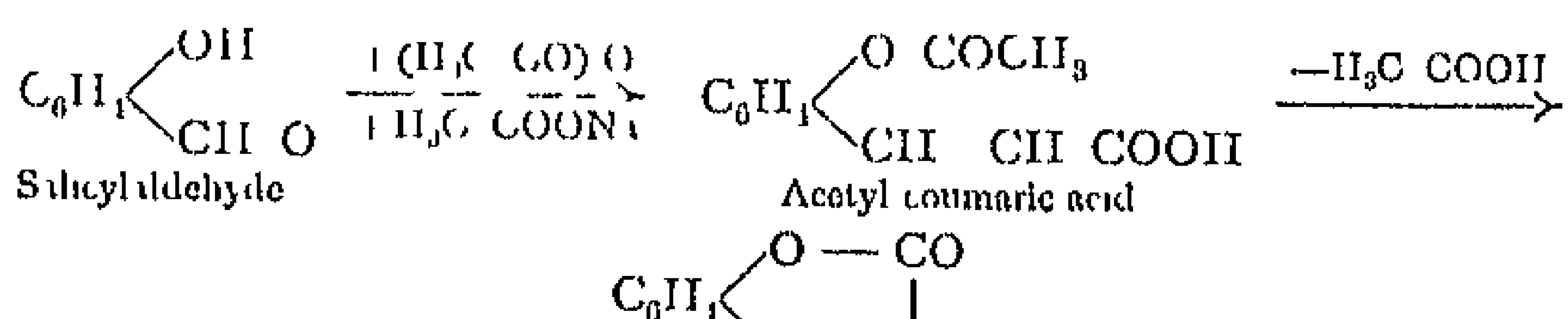
o-**Hydroxy-cinnamic acid**, $HO \cdot C_6H_4 \cdot CH : CH \cdot COOH$, exists in two isomeric forms, distinguished as **coumarinic acid** and *o*-**coumaric acid** respectively.[1] These acids bear the same relationship to one another as maleic and fumaric acids. In coumarinic acid (II.) the groups $HO \cdot C_6H_4$— and —COOH lie on the same side of the molecule (*cis*-form), and in coumaric acid (I.) they are on opposite sides (*trans*-form).



I II III

The chief difference between these compounds is that coumarinic acid in aqueous or alcoholic solution is only stable in the form of its salts, and when liberated in the free state passes at once into the anhydride, *coumarin* (III.). On the other hand, *o*-coumaric acid is readily obtained in the free state. *o*-Coumaric acid occurs in *melilotus officinalis*, and may be prepared from *o*-amino-cinnamic acid by way of the diazo-compound, or from coumarin by boiling with sodium ethoxide. It melts at 208°, is readily soluble in hot water or alcohol, and on reduction with sodium amalgam yields *o-hydrocoumaric* or *melilotic acid*.

Coumarin (formula III. above) is responsible for the perfume of the woodruff (*Asperula odorata*), and occurs also in melilot and in the Tonquin bean. It is prepared by Perkin's reaction (p. 441) by heating salicylaldehyde with acetic anhydride and sodium acetate:



Salicylaldehyde — Acetyl coumaric acid — Coumarin

Homologues of coumarin may be synthesised by the same method, using salts and anhydrides of propionic acid, butyric acid, and so on, in place of those of acetic acid.

Coumarin can also be obtained by the action of sulphuric acid on a mixture of phenol and malic acid (von Pechmann), and substituted coumarins from sulphuric acid, phenols and esters of acetoacetic or monoalkyl-acetoacetic acids.

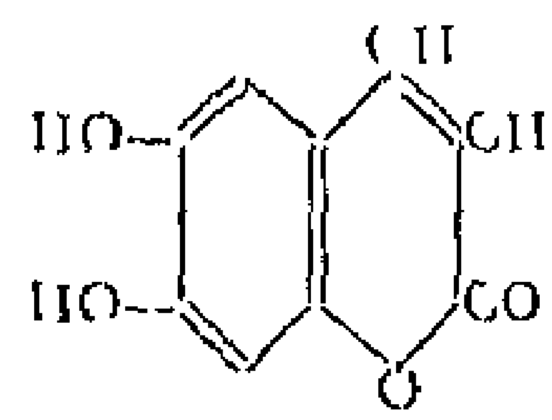
Coumarin is used in the preparation of perfumes (essence of woodruff) and perfumed tobacco.

[1] W. Borsche, *Ber.*, 1904, 37, 346.

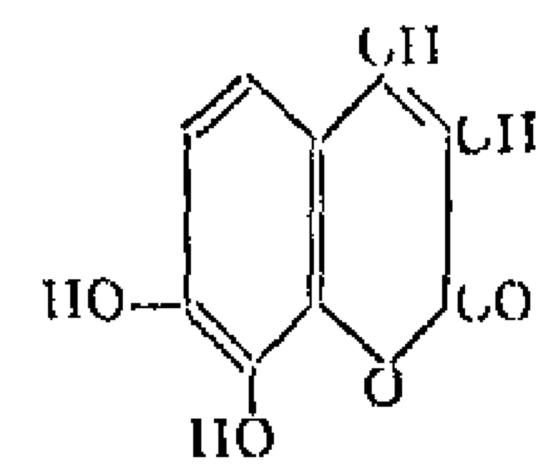
Umbelliferone, 4-hydroxy-coumarin, $HO \cdot C_6H_3\left\langle\begin{matrix}CH:CH\\ \quad\;\; | \\ O\text{—}CO\end{matrix}\right.$, is found in the bark of *Daphne mezereum*, and is produced by the distillation of resins obtained from a number of the *umbelliferæ*. It may be synthesised by Perkin's reaction from β-resorcyl aldehyde, acetic anhydride and sodium acetate, or in a similar manner to coumarin from resorcinol and malic acid. It melts at 240° and is the lactone of *p*-hydroxy-*o*-coumaric acid or *umbellic acid*, $(HO)_2C_6H_3 \cdot CH:CH \cdot COOH$. A structural isomeride of this compound is *caffeic acid*, 3 : 4-dihydroxy-cinnamic acid, the monomethyl ether of which, *ferulic acid*, may be converted into vanillin.

Among substitution derivatives of coumarin may be mentioned the structurally isomeric dihydroxy compounds *aesculetin* (I.) and *daphnetin* (II.).

I



II



The former is a disruption product of the glucoside *aesculin*, occurring in the horse chestnut, and the latter of the glucoside *daphnin*, found in members of the Daphne family. Aesculetin and daphnetin are prepared by Perkin's reaction, by heating hydroxy-hydroquinone aldehyde and pyrogallic aldehyde respectively with acetic anhydride and sodium acetate.[1] They may be regarded as inner anhydrides (δ-lactones) of trihydroxy-cinnamic acids; the latter are not stable in the free state, but only in the form of ether acids or ether esters.

Di- and Trihydroxy Monocarboxylic Acids[2]

Dihydroxy-acids may be derived from the three dihydric phenols, pyrocatechol, resorcinol and hydroquinone. All the six possible isomerides are known.

Protocatechuic acid, $C_6H_3\left\langle\begin{matrix}CO_2H & [1]\\ OH & [3]\\ OH & [4]\end{matrix}\right.$, is formed from various resins (catechu, gum benzoin, myrrh and particularly kino) by fusion with alkali. It may also be obtained from pyrocatechol by heating it to 140° with ammonium carbonate. It crystallises with 1 mol. water, and in the anhydrous state melts at 199°, fusion being accompanied by decomposition into carbon dioxide and pyrocatechol. In aqueous solution protocatechuic acid gives with ferric chloride a green coloration, which on addition of sodium carbonate changes to blue, and finally to red.

According to theory, there should be six possible trihydroxy-benzoic acids, three of which are known.

Gallic acid, 3 : 4 : 5-*trihydroxy-benzoic acid*, $C_6H_2(OH)_3 \cdot COOH$, is found in tea, nut galls, the fruit of *Cæsalpina coriaria* (*Divi-divi*), the

[1] Gattermann and Köbner, *Ber.*, 1899, 32, 289.

[2] Strictly speaking the di- and trihydroxy-cinnamic acids discussed in the previous section should be included here. They are, however, more conveniently treated in connection with coumarin.

root of the pomegranate and in many other plants. It is usually prepared from tannin by boiling with dilute acids, and may be synthesised from bromo-dihydroxy-benzoic acid or bromo-protocatechuic acid by fusion with potash. It dissolves readily in alcohol, ether or boiling water, but is only sparingly soluble in cold water. From the latter it crystallises with 1 mol H_2O. On heating to about 220° it decomposes into carbon dioxide and pyrogallol. Solutions of its alkali salts absorb oxygen from the air and become brown in colour. When gallic acid is treated with potassium persulphate in sulphuric acid it yields **ellagic acid**,[1] $C_{14}H_6O_8$. Gallic acid precipitates gold and silver from their salts and hence can be employed in photography. With ferric chloride it gives a blue-black precipitate. Basic bismuth gallate, $(HO)_3C_6H_2CO_2 \cdot Bi(OH)_2$, is used in medicine under the name of **dermatol**, as an odourless antiseptic in cases of injury or disease of the skin. Bismuth hydroxy-iodide gallate, $(HO)_3C_6H_2CO_2 \cdot Bi(OH)I$, is employed similarly under the name of **airol**.

Orsellinic acid, *4 : 6-dihydroxy-o-toluic acid*, $CH_3 \cdot C_6H_2(OH)_2 \cdot COOH$, is of importance in connection with the chemistry of lichens, from which source it may be extracted. It is prepared by oxidising the readily obtainable orcyl aldehyde,[2] or from the methyl ester of dihydro-orsellinic acid.[3] On partial methylation with diazomethane it yields **everninic acid**, $CH_3O(4) \cdot C_6H_2 \cdot OH(6) \cdot CH_3(2) \cdot COOH(1)$, which is also produced by boiling *evernic* and *ramalic acids* (present in many lichens) with baryta. It forms colourless needles which on rapid heating melt with decomposition in the neighbourhood of 170°.

Depsides [1]

By the combination of phenol carboxylic acids, Emil Fischer has synthesised a number of ester derivatives which he has named *depsides*, because of the resemblance many of them show to the tannins (δέψειν, to tan). According to the number of phenol carboxylic acid molecules united together, these are distinguished as *di-*, *tri-*, *tetra depsides*, and so on. The nomenclature is thus similar to that of the polysaccharides and polypeptides. A simple example of a di-depside is the anhydride of *p*-hydroxy-benzoic acid, formed by the phenolic hydroxyl of one molecule uniting with the carboxyl group of a second to yield the ester, $HO \cdot C_6H_4CO—O \cdot C_6H_4 \cdot COOH$ (depside of *p*-hydroxy-benzoic acid). In a similar manner a third molecule may enter into reaction to give the tri-depside $HO \cdot C_6H_4 \cdot CO—O \cdot C_6H_4 \cdot CO—O \cdot C_6H_4 \cdot COOH$.

Fischer prepared the above compounds as the result of an observation made during the synthesis of polypeptides of tyrosine, for which

[1] For the constitution of this acid, see A. G. Perkin and Nierenstein, *Proc. Chem. Soc.*, 1905, 21, 185; Herzig and Pollak, *Monats.*, 1908, 29, 263; Graebe, *Ber.*, 1903, 36, 212. [2] Hoesch, *Ber.*, 1913, 46, 886. [3] A. Sonn, *Ber.*, 1928, 61, 926. [1] E. Fischer, *Ber.*, 1913, 46, 3253; 1919, 52, 809; P. Karrer and Salomon, *Helv. Chim. Acta*, 1922, 5, 108; 1923, 6, 3.

the acid chloride of chloracetyl-tyrosine was required It appeared probable that the free phenolic group of the acid might cause trouble owing to the necessary treatment with phosphorus chloride, and it was therefore protected by the introduction of another group which could later be removed without difficulty For this purpose the carbomethoxy group was selected Later the same process was applied to the phenol-carboxylic acids and led to the synthesis of depsides In place of the carbomethoxy compounds first employed, Fischer later used acetylated phenol-carboxylic acids in this work

Carbomethoxy Derivatives of Phenol-carboxylic Acids—These are readily obtained by the combined action of methyl chloroformate and alkali on phenol-carboxylic acids in cold aqueous solution[1] The reaction proceeds particularly smoothly when the phenolic group is in the *m*- or *p* position to the carboxyl group, *e g* *p*-hydroxy-benzoic acid readily yields carbomethoxy-*p*-hydroxy-benzoic acid, $CH_3O \cdot CO \cdot O \cdot C_6H_4 \cdot COOH$

Chlorides of carbomethoxy-phenolcarboxylic acids are obtained by the action of phosphorus pentachloride on the acids They are usually crystalline and have most of the properties of benzoyl chloride Since the carbomethoxy group can easily be removed, they are of great value for further synthesis

Conversion of the Chlorides into Depsides—The acid chlorides may be combined with free phenol-carboxylic acids, and on subsequent removal of the carbomethoxy group di-depsides are produced By repeating this process tri- and tetra-depsides may be obtained For example, the chloride of carbomethoxy-*p* hydroxy-benzoic acid unites with *p*-hydroxy-benzoic acid in the presence of cold aqueous alkali to form the salt of carbomethoxy p-*hydroxybenzoyl-hydroxy-benzoic acid*

$$CH_3O \cdot CO \cdot O \cdot C_6H_4 \cdot CO \cdot Cl + NaO \cdot C_6H_4 \cdot COONa$$
$$= NaCl + CH_3O \cdot CO \cdot O \cdot C_6H_4 \cdot CO \cdot O \cdot C_6H_4 \cdot CO_2Na$$

On treatment with mineral acid this salt yields the free acid

Removal of the Carbomethoxy Group—This may be effected by means of cold dilute alkali or ammonia

By these methods Fischer has prepared numerous depsides and some tri and tetra-depsides, including the di-depsides, *lecanoric acid* and *evernic acid*, which are present in lichens

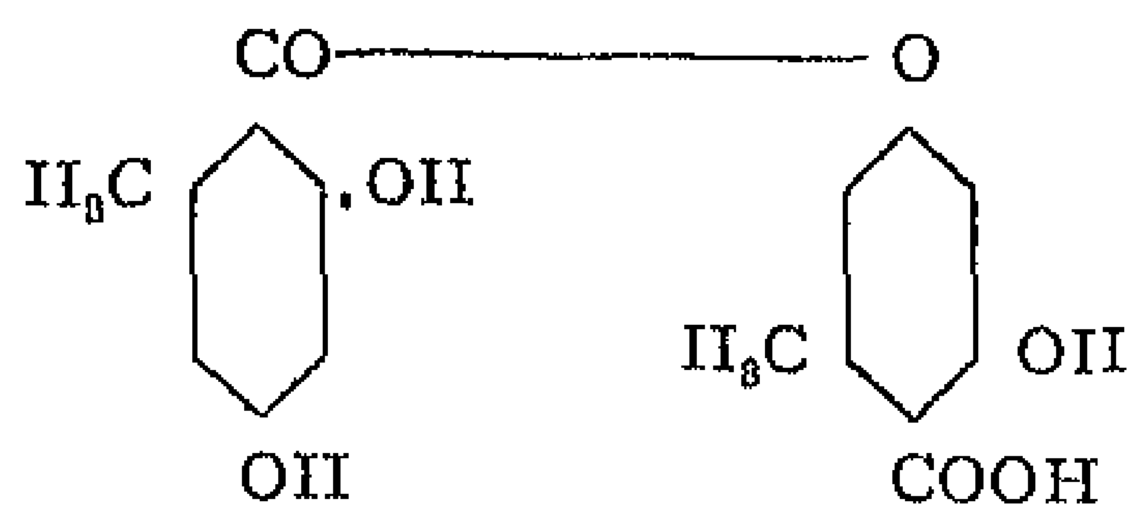
Properties of Depsides—All depsides are decomposed into their components by an excess of dilute alkali, even at the ordinary temperature The di-depsides of gallic, protocatechuic, gentisic and β-resorcylic acids precipitate dilute solutions of glue, and give a precipitate with quinine acetate even at high dilutions In this property they differ from the parent phenol-carboxylic acids and resemble the tannins

[1] E Fischer, *Ber*, 1908, 41, 2875

Depsides in Lichens[1]

So far as is known, the lichens form the only natural source c depsides Lichens are a result of the symbiosis (lit *living together* of algæ and fungi, and their peculiar morphological character goe hand in hand with their unusual chemical composition, as shown i their content of depsides Among the latter the best know representative is lecanoric acid

Lecanoric acid,[2] p *di-orsellinic acid*, is a di-depside of the formula



It may be isolated from various lichens, and has been synthesise by methods already described from orsellinic acid Lecanoric acid i sparingly soluble in water, but dissolves more readily in ether (1 30 In the dry state it melts with decomposition at about 166°

Evernic acid, monomethyl-lecanoric acid, contains a methoxyl i the *p* position to the depside group (see previous formula), since th everninic acid obtained (together with orsellinic acid) from it o hydrolysis has been shown to be *p*-methyl orsellinic acid It can b synthesised from everninic and orsellinic acids by the same method as were used for lecanoric acid

THE TANNINS[3]

Under this name are included numerous vegetable product possessing the common property of combining with animal hide t render it pliant and non putrescible When an attempt is made t classify these substances from the chemical standpoint, it is found tha they fall into a number of quite different groups Those best investi gated are the tannins of the tannic acid class, which may be describe shortly as esters derived from sugars by union with phenol-carboxyli acids

The typical and most important tannin is **tannic acid** This i closely related to *gallic acid*, and is present in large amount (abou 50 per cent) in gall-nuts, which are pathological growths on the leave and twigs of trees of the oak family, due to the puncturing of th tissues by the gall wasp In addition it is found in sumach, tea an many other plants It is best prepared from finely-divided gall

[1] E Fischer, *Ber*, 1913, 46, 3269 A Sonn, *Ber*, 1928, 61, 2479 [2] E Fischer an H O L Fischer, *Ber*, 1913, 46, 1138 [3] Freudenberg, *Die Chemie der natürlichen Gerbstoff* Berlin, 1920

nuts by extraction with a mixture of ether and alcohol. Even after the most careful purification, commercial tannic acid is not a homogeneous compound but a mixture.

Pure tannic acid is a colourless amorphous substance, which dissolves readily in water and sparingly in alcohol and ether. The aqueous solution possesses a bitter astringent taste and is coloured dark blue by ferric salts, hence its use in the manufacture of ink.[1] Tannic acid is withdrawn from its aqueous solution by animal hide, the latter being "tanned" and converted into leather (see p. 457). Tannin also precipitates many alkaloids and proteins from their solutions. This reaction provides one of the most sensitive tests for proteins.

The work of E. Fischer has thrown much light on the constitution of tannins from the leaf gall of *Rhus Semialata* (Chinese tannin) and the twig gall of *Quercus infectoria* (Turkish tannin). The last details of their constitution will probably remain unsolved for some time yet, as these amorphous products appear to be inseparable mixtures of very closely related poly galloyl-glucoses.

Fischer has also synthesised other depsides or ester compounds of glucose with phenol-carboxylic acids. Of these, *1-galloyl-β-glucose*, $C_6H_{11}O_5 \cdot O \cdot CO \cdot C_6H_2(OH)_3$, was identified with the *glucogallin* of Chinese rhubarb.[2] The work culminated in the synthesis of penta-*m*-digalloyl-β-glucose, $[(HO)_3C_6H_2 \cdot CO \cdot O \cdot (HO)_2C_6H_2 \cdot CO]_5 \cdot C_6H_7O_6$, which shows a strong resemblance to Chinese tannin, of which it may possibly be the chief constituent.[3]

Turkish tannin is less homogeneous than that from Chinese galls, as it also contains a compound of ellagic acid which is readily soluble in water. In this tannin the greater part of the gallic acid is united to sugar in the form of galloyl groups, because on methylation and hydrolysis with alkali only a small proportion is recovered as *m*, *p*-dimethyl-gallic acid, the greater part being obtained as trimethyl-gallic acid. The phenolic hydroxyl groups are therefore almost entirely free in Turkish tannin, and the galloyl groups must be largely present as such and not in the form of condensed groups such as digalloyl. The relative proportion of sugar to gallic acid is considerably larger than in Chinese tannin, 1 mol. glucose corresponding to about 5 or 6 mols. gallic acid.

[1] Ordinary writing inks commonly consist of a solution containing tannic acid (or aqueous extract of gall nuts) and ferrous sulphate, together with certain acidic substances, gum, and phenol (to prevent mouldiness). The ferrous salt of tannic acid is first formed, or the tannic acid may become hydrolysed, giving the salt of gallic acid. These salts are soluble and only feebly coloured, and the small amount of acid (HCl or H_2SO_4) present prevents the untimely precipitation of black ferric compounds. When used for writing the acidity of the ink is neutralised by the alumina present in the paper. Oxidation then occurs and a black insoluble iron precipitate, stable to light, is formed. Owing to the pale colour of the unoxidised ink it is usual to add dyes, such as soluble indigo or aniline blue, to the above mixtures. [2] *Ber.*, 1919, 52, 818. [3] *Ber.*, 1918, 51, 1760; P. Karrer, *Helv. Chim. Acta*, 1923, 6, 3.

Hamameli tannin,[1] obtained from the bark of *Hamamelis Virginica*, crystallises well and may be regarded as homogeneous It forms colourless needles of $[\alpha]^{20}_{D} = +35.6°$ in 1 2 per cent aqueous solution In place of glucose it contains some other hexose combined with gallic acid in the form of an ester, as in the gallotannins None of the phenolic groups are substituted and each galloyl residue is united through the carboxyl to a hydroxyl group of the sugar From the degradation of hamameli tannin by fermentation the proportion of gallic acid to hexose has been found to be 2 1 Analytical results agree with a di galloyl hexose

The discovery that ester compounds of sugars with phenolic carboxylic acids constitute a large class of tannins is of great importance in connection with plant physiology It is of particular interest that the sugar of the plant is used in the same way as glycerol and the monohydric alcohols in the esterification of acids

Tannic acid is employed as a medicament, in the preparation of inks, as a mordant in dyeing, and for the clarification of wine

Tannigen, apparently prepared by heating tannic acid with acetic anhydride and ethyl acetate, is probably a diacetyl tannin It is used medicinally in cases of chronic diarrhoea

A number of other naturally occurring tannins have as yet been little investigated These are usually named after the plant in which they occur They all dissolve readily in water, possess a bitter taste, give a dark blue or green colour with ferric salts, are precipitated with lead acetate solution, precipitate proteins and transform animal hide into leather Some of these compounds are glucosides of gallic or other closely related acids

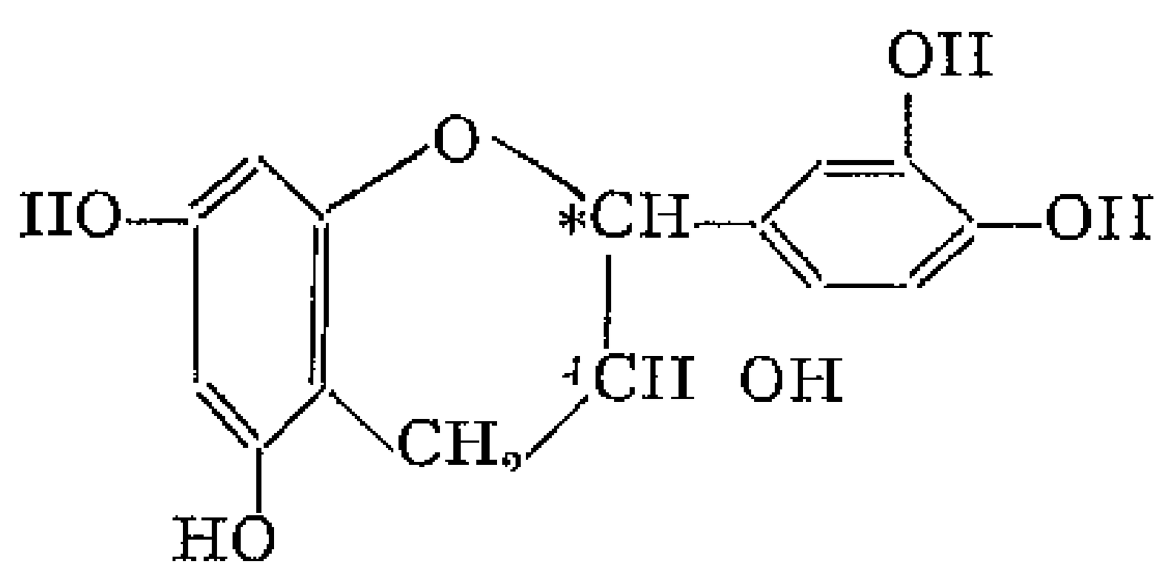
Among such substances may be mentioned *kino tannin*, the chief constituent of kino, *moringa tannin* or *maclurin*, extracted from the yellow wood of *Morus tinctoria* by means of hot water, the tannin of coffee, occurring in coffee beans and Paraguay tea, and *oak tannin*, occurring in the bark of oak From cinchona or Peruvian bark is obtained a tannin which is present in combination with the cinchona alkaloids The commercially valuable *tannin of the chestnut* is related to that of the native oak when treated with dilute mineral acids it yields ellagic acid, glucose and traces of gallic acid Its behaviour on fermentation appears to exclude it from the class of ester tannins, to which the gallo tannins belong, and it also shows no similarity to the catechins, since it contains no phloroglucinol, is strongly acidic and is almost insoluble in ethyl acetate [2]

Catechins — This group includes a number of isomeric compounds of the composition $C_{15}H_{14}O_6$ which are present in *cutch* or *catechu*, a product prepared from various plants by extraction with hot water *Gambier catechu* is obtained from the bush *Uncaria gambier* (Malacca, Penang, Singapore), *Bengal* or *acacia catechu* from the wood of *Acacia catechu* (India, Burma), *Bombay* or *areca catechu* from the fruit of the betel nut palm tree, *Areca catechu* (Asia), and *mangrove cutch* from the bark of the mangrove, *Ceriops candolleana* The pure catechins are

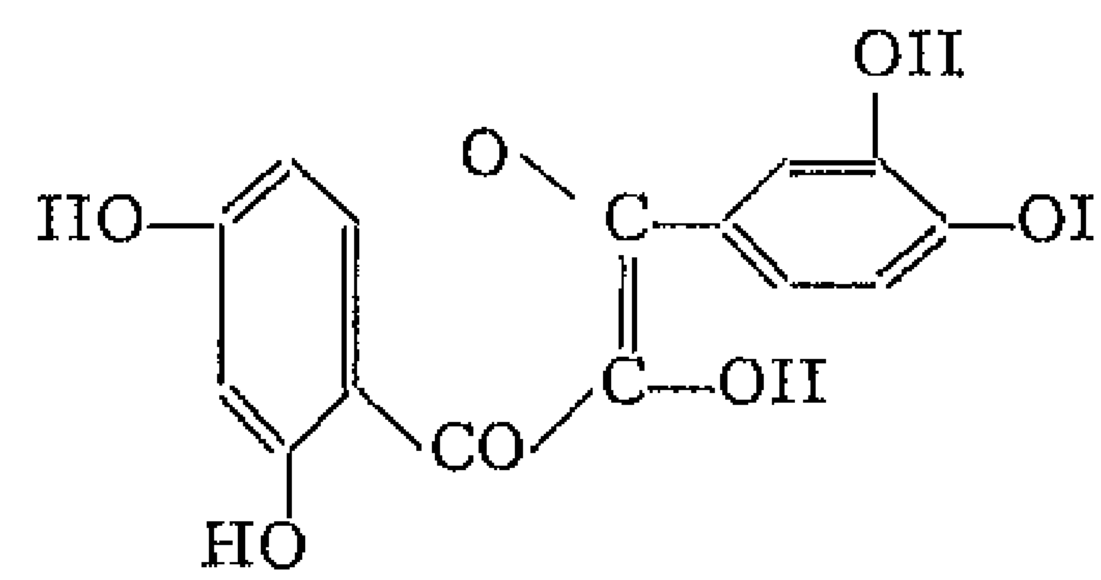
[1] K Freudenberg, *Ber*, 1919, 52, 177, 1920, 53, 953 *Ann*, 1924, 440, 5 [2] K Freudenberg and H Walpuski, *Ber*, 1921, 54, 1695

colourless crystalline derivatives of phloroglucinol They form the basis of many natural tannins, and under the influence of mineral acids, enzymes or heat they readily change into amorphous tannins or tannin reds

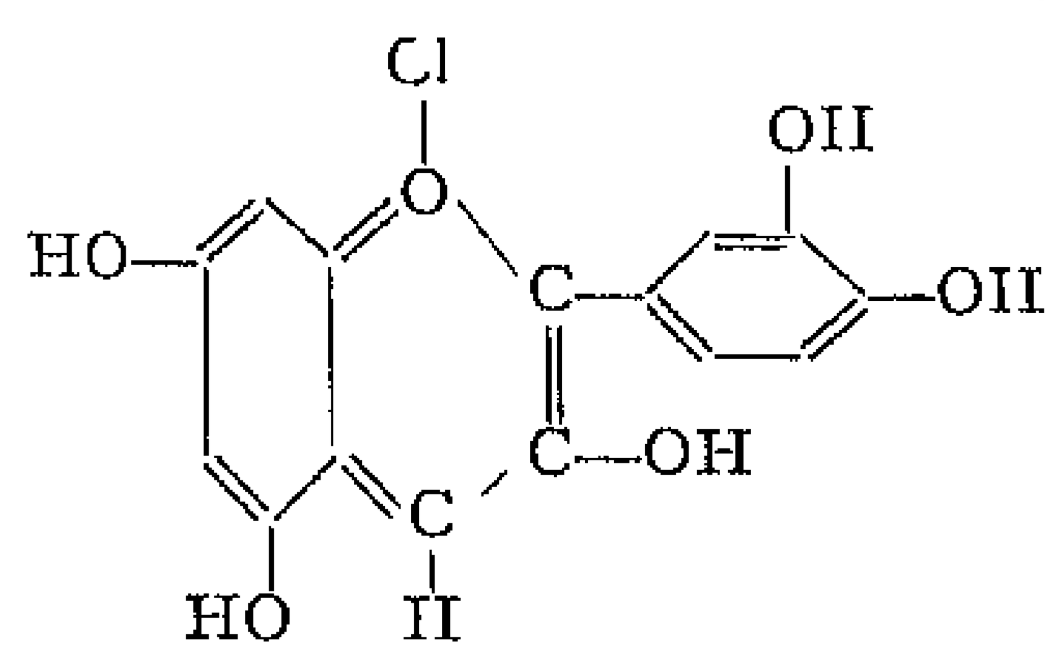
The constitution of these compounds has proved an exceedingly difficult problem, but the researches of Freudenberg, based on earlier work of Kostanecki and of A G Perkin, have now shown the catechins to be isomerides of the following structure I This constitution is closely related to that of the flavone dye-stuffs[1] (*e g* quercetin II) and the anthocyanidins (*e g* cyanidin chloride III) The relationship to the natural flower pigments was proved[2] by the conversion of cyanidin chloride (p 786) into *r epi*catechin by reduction in alcoholic solution, using platinum black and hydrogen



I Catechin



II Quercetin



III Cyanidin chloride

As may be seen from formula I, these compounds may exhibit *cis* and *trans* isomerism due to a different arrangement of the groups around the two C-atoms marked * Catechin itself is believed to be of the *trans* type, and the more recently discovered *epi*catechin of the *cis* variety In addition the two marked atoms are asymmetric, thus giving rise to optically active and racemic forms of catechin and *epi*catechin

It appears that, owing to the crude methods in use, a certain amount of *cis-trans* isomerisation and racemisation occurs during the process of extraction Freudenberg and Purmann[3] carefully extracted acacia heart-wood at a low temperature and found the product to consist almost entirely of *l epi*catechin and a little *r* catechin The technical

[1] Formula I for catechin and the relationship to quercetin were first suggested by A G Perkin and Yoshitake, *J C S*, 1902, 81, 1162, 1905, 87, 398 [2] Freudenberg and co workers, *Ann*, 1925, 444, 134 [3] *Ann*, 1924, 487, 274

product from this source examined by A G Perkin,[1] and named by him *aca*catechin, has been found to be a mixture of stereoisomerides (*i*-catechin, together with *l* catechin, *l-epi*catechin and *r epi*catechin), formed apparently by the transformation of *l epi*catechin

A red amorphous substance known as **catechutannic acid** is present in small amounts in *Gambier catechu*, and in considerably larger quantities in the browner varieties of cutch It is believed to be an anhydride of catechin and is a powerful tanning agent

Cutch or catechu is also used as a dye, giving a fast brown colour on cotton For this purpose it is employed in combination with copper sulphate followed by treatment with potassium bichromate It is also used as a preservative for fishing nets, sailcloth, etc

Tanning of Hides

Animal skins rapidly putrefy in the moist state, and on drying become stiff and hard By tanning they may be converted into leather, which resists decay and remains pliable when dried According to the materials employed, a distinction is drawn between *bark*, *mineral* and *oil tanning* It is mainly in the first and oldest of these processes that the tannins are used [2]

The materials used as sources of the tannins are as follows oak bark, pine bark (Saxony, Hungary), hemlock fir (North America), larch (England), birch and willow (Russian leather, Swedish and Danish glove leather) A wood rich in tannins is *quebracho* wood, containing on the average 20 per cent of tannin, extracts of which are imported in considerable quantities from the Argentine Extracts from wood of the oak and chestnut, and also from various barks, are made by treatment with hot water and subsequent concentration Such extracts are employed on a large scale

The skins must first be prepared and rendered capable of readily absorbing the tanning liquor Of the two main layers of which the hide consists, viz the epidermis (outer layer) and the corium or dermis (true skin), the latter alone is required The fresh skin is therefore hung in running water to remove blood and dirt, and the hair and epidermis loosened by treatment with lime, sulphides, or decomposing dung, which also makes the texture more open The epidermis and hair are then removed by scraping with blunt tanners' knives

The subsequent tanning process may be effected with tan bark, which takes a considerable time, or may be completed much more rapidly by the use of *tannin extracts* In the former method the skins are hung in pits containing tan liquor of greater and greater concentration over a period of six to eight weeks, and are then transferred to the "layers" In these the skins are placed in layers, each being dusted over with the solid tanning material and the whole covered with strong tan liquor The liquor is usually withdrawn and renewed several times, the length of treatment varying with the thickness of the hide from three to six months or more

With the aid of tannin extracts, on the other hand, a skin may be completely tanned in from two to twelve weeks, according to thickness

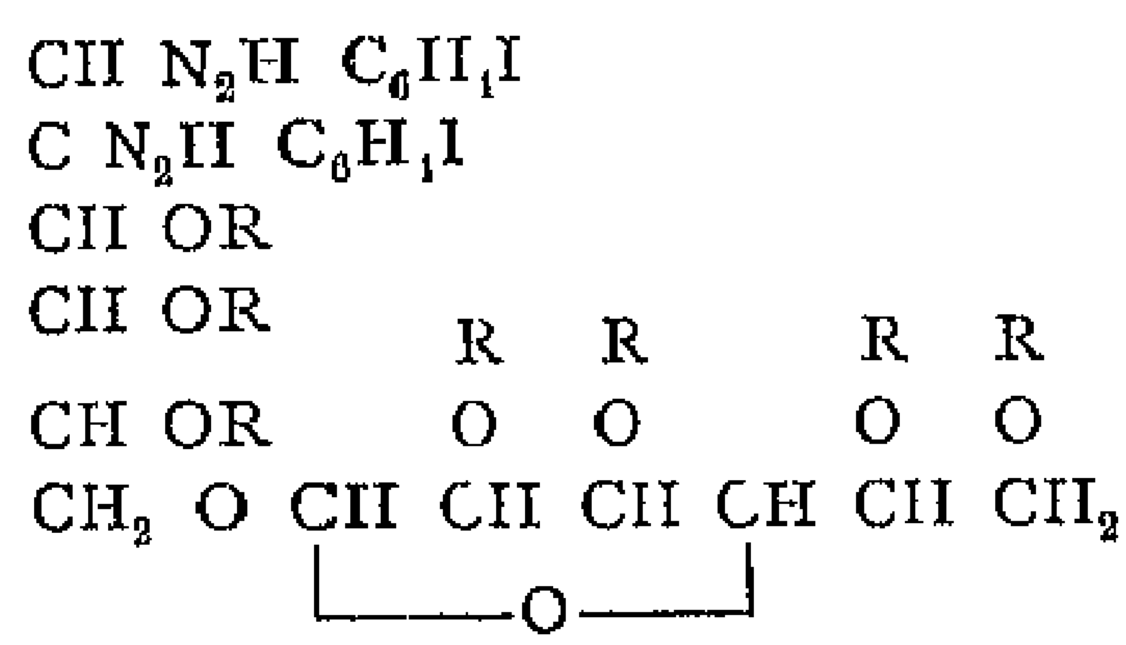
[1] *J C S*, 1902, 81, 1160, 1905, 87, 404 [2] *Oil tanning* (for chamois leather) is effected with the aid of fish oil, in mineral tanning use is made of a solution of alum and common salt (*alum tanning*), basic chromium salts (*chrome tanning*), or iron salts Chrome tanning has recently become a serious rival to vegetable tanning

Certain tannin substitutes have recently come into use, such as *neradol* (a condensation product of phenol sulphonic acid with formaldehyde), *neradol D*, and *ordoval*.

It has not yet been determined with certainty whether the tannin is deposited mechanically in the hide or enters into chemical combination with it. The changes taking place probably follow in the main the laws of colloid chemistry.

High Molecular Products[1]

Synthetic products of very high molecular weight have already been described under the depsides and tannins. The preparative methods there described permit the synthesis of compounds of much higher molecular weight than the tannins, and in order to see how far this compression of matter could be carried, E. Fischer coupled up *p*-iodophenyl-maltosazone with tribenzoyl-galloyl-chloride. In this manner hepta-(tribenzoyl-galloyl)-*p*-iodophenyl maltosazone was formed, a compound containing 426 atoms in the molecule and having the molecular weight 4021.



$R = CO \cdot C_6H_2(O \cdot CO \cdot C_6H_5)_3$

Hepta-(tribenzoyl galloyl) *p*-iodophenyl-maltosazone, $C_{220}H_{142}O_{58}N_4I_2$

"With this number (mol. wt. 4021)," writes Fischer, "the compound stands at the head of all organic substances of known structure and is, in addition, accessible by complete synthesis." In the size of its molecule it is several times larger than the highest product of polypeptide synthesis, and in this respect may even exceed the majority of the natural proteins.

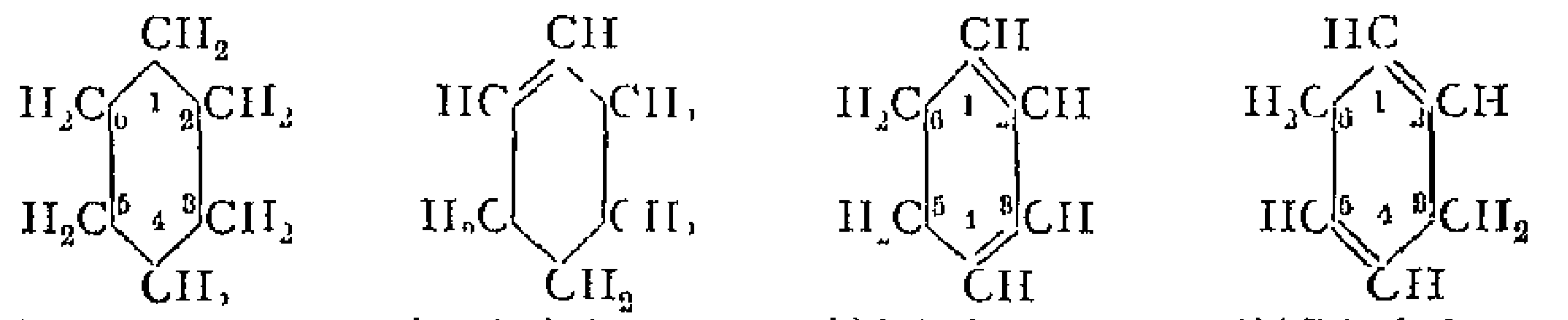
XII

Hydroaromatic Compounds

Benzene and its derivatives can take up hydrogen, without disruption of the six-membered ring, to form hydroaromatic compounds. Although the latter possess the same ring structure as the aromatic compounds, they differ from them in many points and show more resemblance to the aliphatic series. The carbon ring of hexahydrobenzene, or hexamethylene, exhibits approximately the same degree of stability as that

[1] F. Fischer and K. Freudenberg, *Ber.*, 1913, 46, 1116, 3287.

of pentamethylene (p 350), and these compounds and their derivatives behave in the main like the paraffins—although somewhat more reactive in consequence of their cyclic structure On the other hand, tetrahydrobenzene and the dihydrobenzenes correspond to the olefines



Hexahydrobenzene Tetrahydrobenzene $\Delta^{1,3}$ Dihydrobenzene $\Delta^{1,4}$ Dihydrobenzene

Only one tetrahydrobenzene exists but two dihydrobenzenes are possible Numerous cases of isomerism occur among derivatives of these hydrocarbons according to the position of the double bond or bonds, which must therefore be indicated For this purpose the six carbon atoms of the hexagon ring are numbered and the position of a bond indicated by the Greek letter Δ, to which is attached an index number corresponding to the first atom of the doubly linked pair, as illustrated in the above formula

The hydrobenzenes and their derivatives are described in the succeeding pages, a separate section being devoted to the terpenes, which are derived from reduced cymenes

Many hydroaromatic compounds are distinguished by the ease with which they may be transformed into the corresponding aromatic substances

I—HYDROCARBONS, ALCOHOLS, KETONES, ALDEHYDES AND ACIDS OF THE CYCLOHEXANE SERIES

Occurrence—Hydrocarbons of the cyclohexane series are present in considerable quantities in Caucasian petroleum The mixture of hydrocarbons known as **naphthenes**, obtained by fractionating the petroleum, consists mainly of cyclopentanes and cyclohexanes [1]

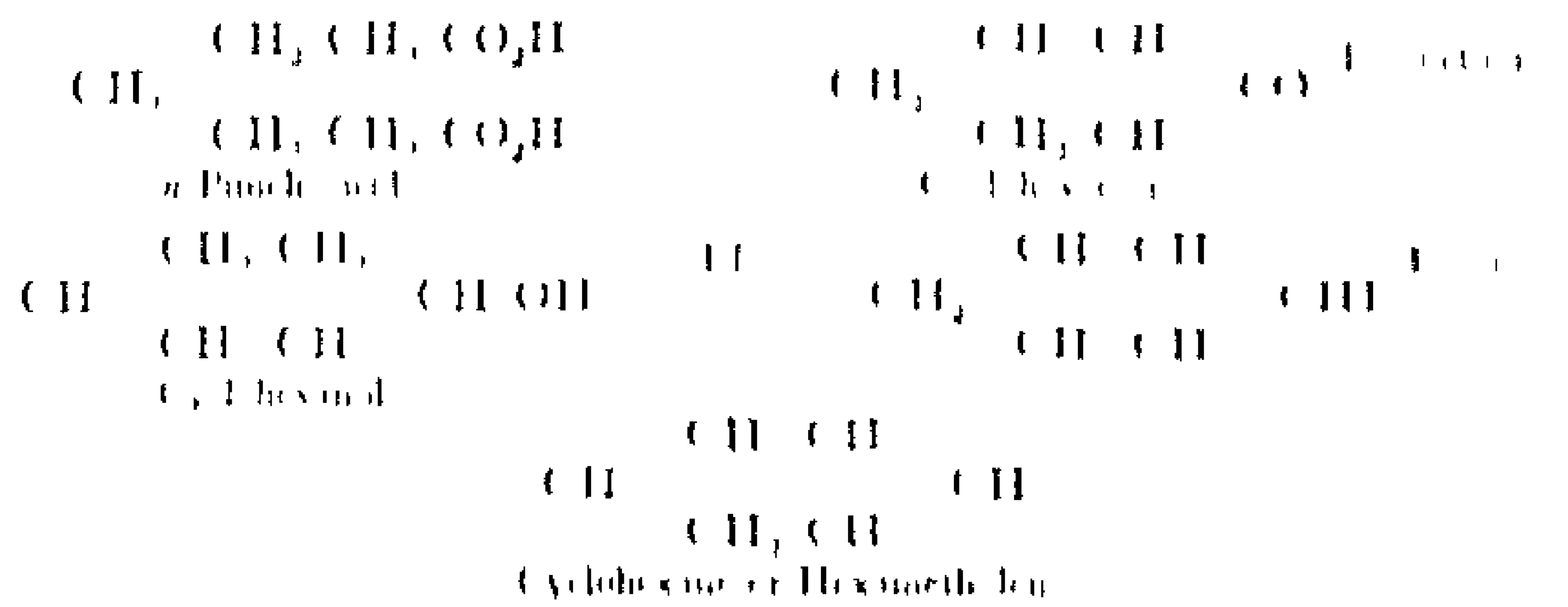
Formation—A number of methods of synthesising hexamethylene derivatives have already been described and these may be briefly summarised

Many have been prepared by reduction of the corresponding benzene compounds, recently with the use of metals of the platinum group as catalysts The method of Sabatier and Senderens (passing the vapour of the substance, mixed with hydrogen, over heated, finely-divided nickel) may also be satisfactorily employed for this purpose [2]

In other methods aliphatic compounds form the starting-point Cyclic ketones, as already explained, are produced by distilling the calcium salts of dibasic acids, cyclohexanone, for example, being

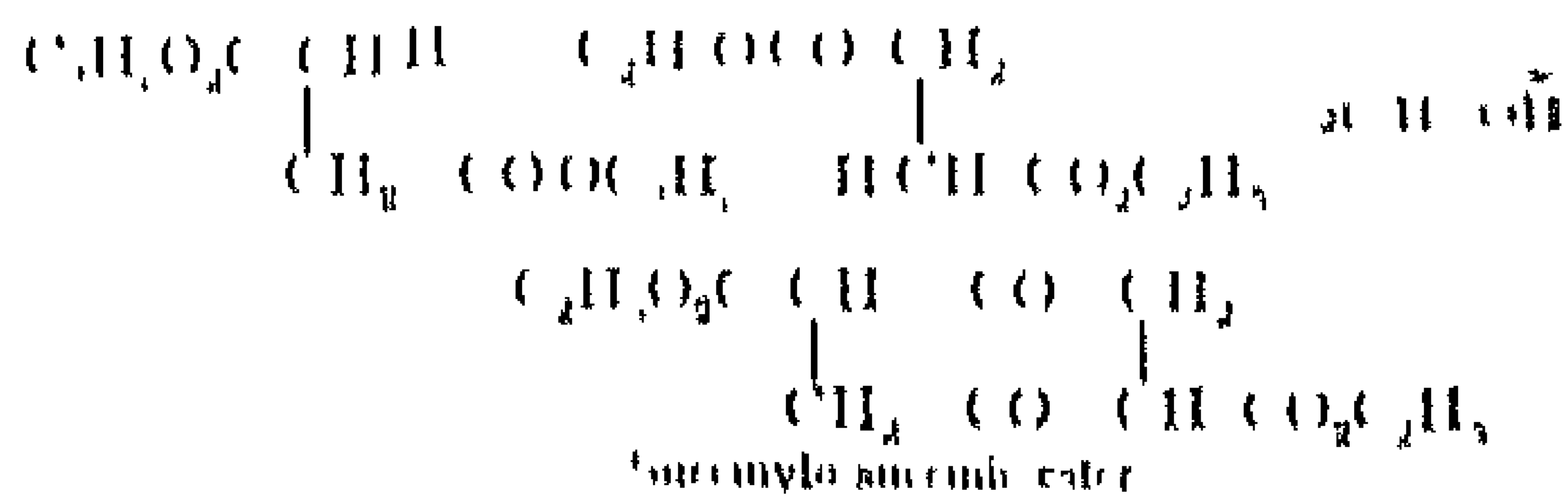
[1] For the origin of naphthenes and naphthenic acids, see O Aschan, *Ann*, 1902, **324**, 1 For the constitution of *naphthenic acids*, see also N Zelinsky and E Pokrowskaja, *Ber*, 1924, **57**, 51 [2] Sabatier and Mailhe, *C*, 1906, I, 1248 Sabatier, *Ber*, 1911, **44**, 1984 Zelinsky, *Ber*, 1911, **44**, 2779, 3121, 1925, **58**, 1298

obtained from calcium pimelate. Hexamethylene itself was first synthesised by Baeyer in the following way:



Later it was also prepared from hexamethylene dibromide by reduction with sodium.

An interesting reaction, already mentioned on p. [illegible] (see also Ester Condensations, p. [illegible]), consists in the conversion of diethyl succinate into *succinylo succinic ester* by treatment with metallic sodium. This substance serves for the preparation of further hexamethylene derivatives:



Finally it may be noted that the Grignard reaction has also been applied with success to syntheses in the cyclohexane series.

By the distillation of coal *in vacuo*, A. Pictet and M. Bouvier[1] obtained a tar from which two hydrocarbons, $C_{10}H_{20}$ and $C_{11}H_{22}$, were isolated. They also isolated the same hydrocarbons from Canadian petroleum, thus establishing an experimental connection between these two natural products. The hydrocarbon $C_{10}H_{20}$ from the above vacuum tar boils at 17[illegible]° to 17[illegible]°, and is most probably *hexahydro-durene* (1, 2, 4, 5-tetramethylcyclohexane), while the compound $C_{11}H_{22}$, b.p. 189° to 191°, is probably the *hexahydride of pentamethyl-benzene*.

Cyclohexane and its Derivatives

Hexahydrobenzene, *hexamethylene, cyclohexane, naphthene*, C_6H_{12}, is formed by the above reactions and may be obtained from pure benzene by reduction with platinum and hydrogen.[2] It is an important constituent of Caucasian petroleum and is a colourless liquid, b.p. 81°

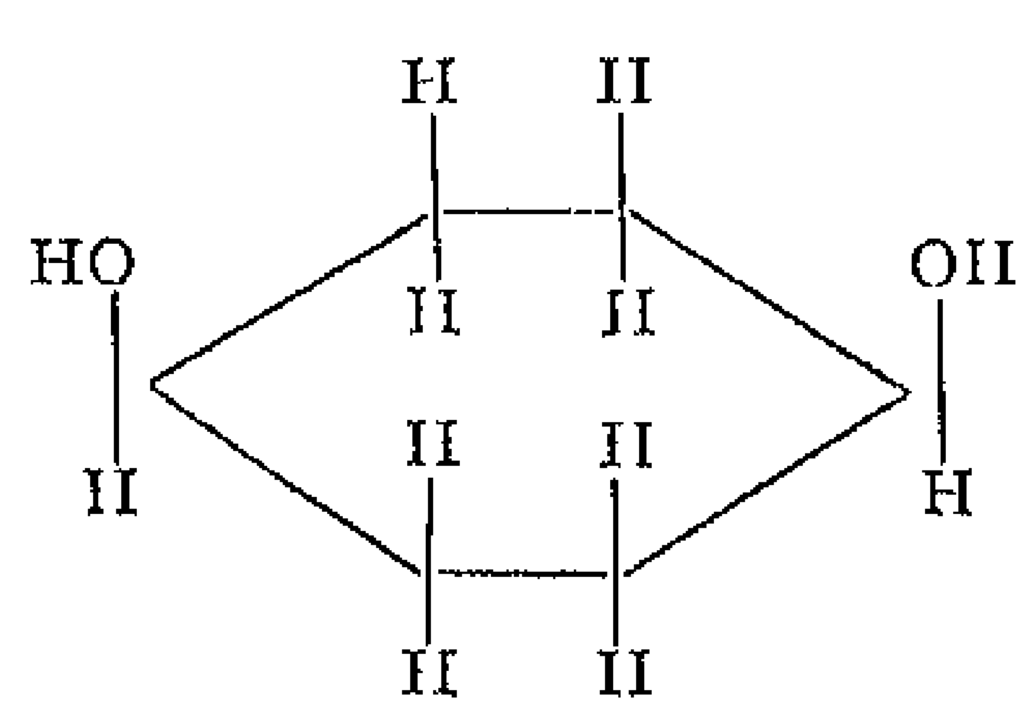
[1] *Ber.*, 1913, 46, 3342. [2] Willstätter and Hatt, *Ber.*, 1912, 45, 1471. [3] [illegible], *Ber.*, 1913, 46, 3342.

(corr.) and m.p. 6·4°, with a smell like benzine. A characteristic property is the ease with which it is oxidised to adipic acid by nitric acid. *Benzene hexachloride*, $C_6H_6Cl_6$, a chloro-derivative of hexamethylene, is formed by leading chlorine into benzene, and exists in two modifications (m.p. 157° and 310°). *Monochlorohexamethylene* is readily prepared by the action of chlorine on hexamethylene. Unlike alkyl halides, these monochloro- and bromo-derivatives do not yield alcohols when treated with alkalis, but form **tetrahydro-benzene**, C_6H_{10}. The latter is a colourless liquid boiling at 83° to 84° (743 mm.). Amino-derivatives of hexahydrobenzene resemble aliphatic amines in their behaviour.

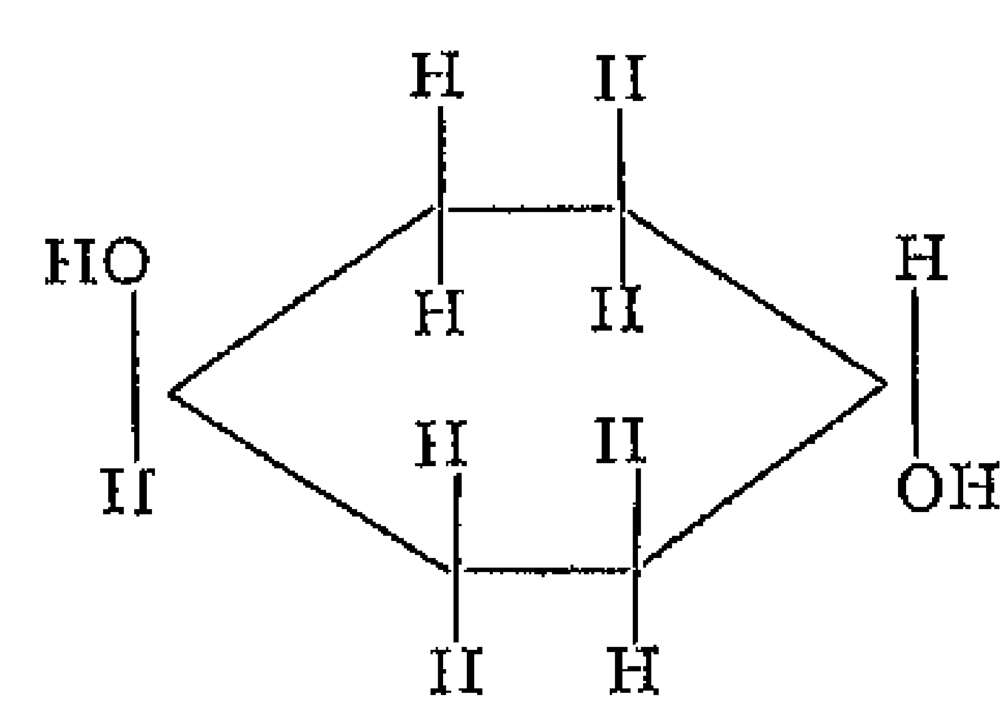
Hexahydrophenol, *cyclohexanol*, $C_6H_{11}\cdot OH$, is produced in good yield by leading a mixture of phenol vapour and hydrogen over finely-divided nickel at 140° to 160°. It is a colourless liquid, b.p. 160·5°, which solidifies at a low temperature to a mass of melting-point 20°. With hydrobromic acid it yields the above-mentioned *monobromo-cyclohexane*, b.p. 162°, and with hydriodic acid *mono-iodo-cyclohexane*, b.p. 180°. When hexahydrophenol is heated with oxalic acid, water is eliminated and tetrahydrobenzene formed.

Quinitol, *cyclohexane-1 4-diol* (hexahydro-hydroquinone), was obtained by Baeyer, by reducing *p*-diketo-hexamethylene (see p. 463) with sodium amalgam. It exists in two stereoisomeric forms.

This type of isomerism is similar to that described under fumaric and maleic acids (p. 49), the ring structure hindering free rotation of the carbon atoms in the same manner as the double bond of the ethylene series. Polymethylene derivatives thus exhibit stereo-isomerism due to the different spatial positions of the atoms with reference to the plane of the ring, exactly analogous to the geometrical isomerism of ethylene compounds, in which the atoms occupy different positions in space as referred to the plane of the double bond. Theory therefore predicts that each disubstitution product of a polymethylene should exist in two stereoisomeric forms, according as the substituent atoms or groups lie on the same or on opposite sides of the plane of the ring. In agreement with this, two isomeric quinitols are known, corresponding to the formulæ:



cis-Quinitol, m.p. 102°



trans-Quinitol, m.p. 139°

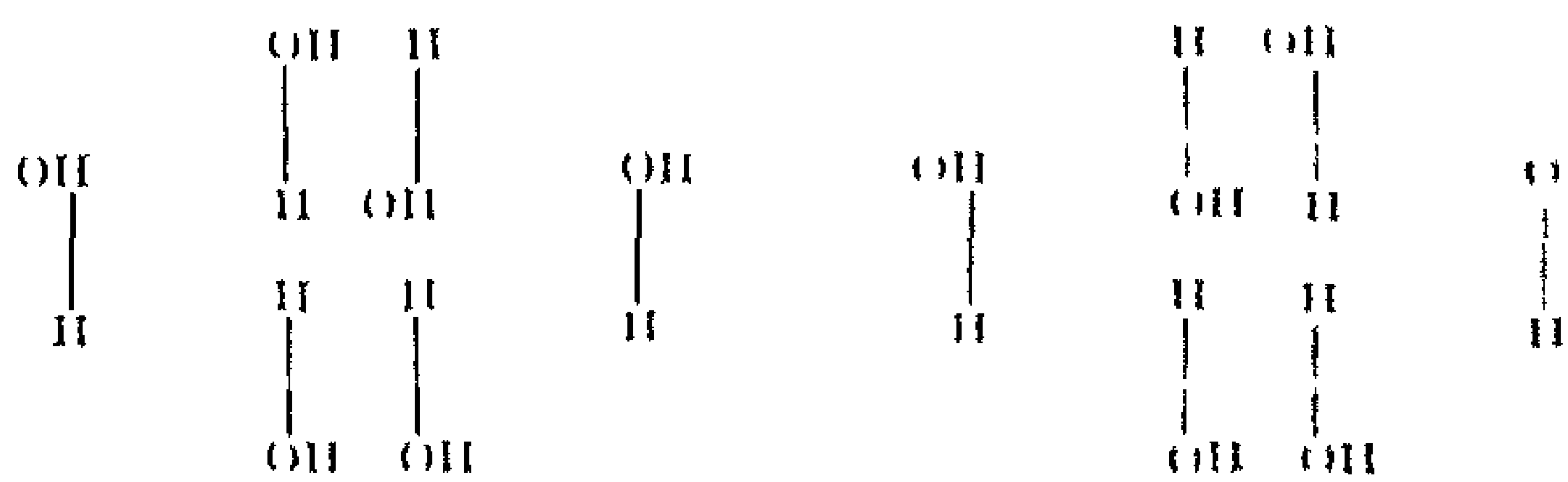
These differ in their configuration in such a way that in [illegible] the hydroxyl groups lie on the same side, and in [illegible] opposite side of the plane of the ring.[1]

Quercitol, *cyclohexanepentol*, $C_6H_7(OH)_5$, [illegible] active form in acorn (*Quercus* [illegible]). It melts at [illegible].

Inositol, *cyclohexanehexol*, $C_6H_6(OH)_6$, [illegible] form, a racemic and two optically active forms. It [illegible] muscle of the heart, in liver and in various plants. It [illegible] same empirical formula as the hexoses, which it [illegible] having a sweet taste.

The active inositols (d and l) are of interest [illegible] known optically active compound containing no asymmetric atom.

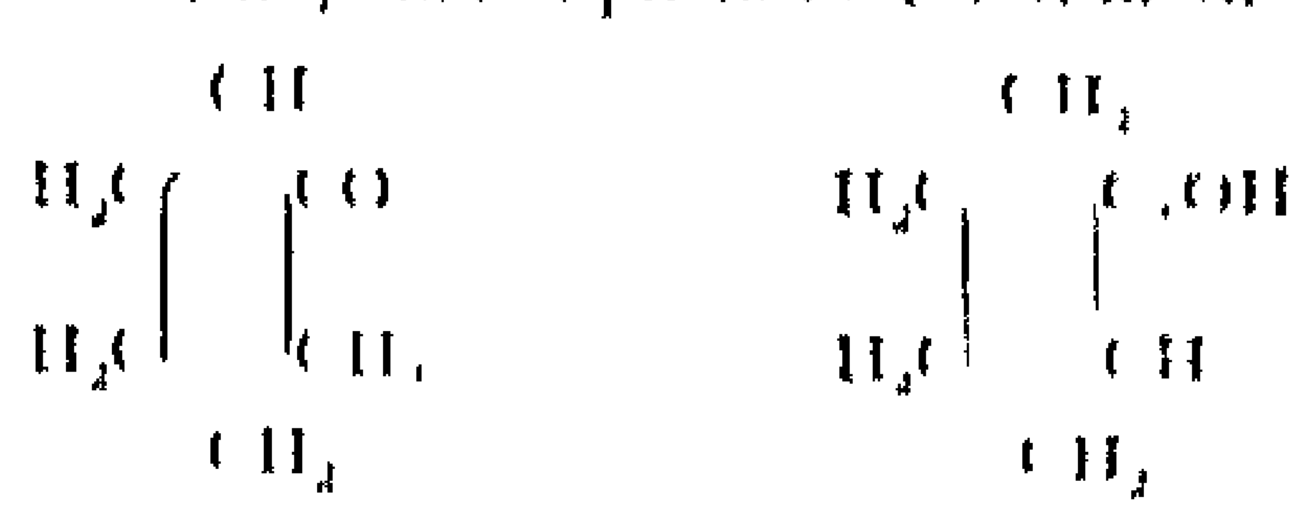
Their configurations have been represented by [illegible] in the following manner:



since of the nine theoretically possible [illegible] of hexahydroxy-cyclohexane only these two mirror-image structures are without a plane of symmetry.

Keto-hexamethylene, *cyclohexanone*, is formed by heating the calcium salt of n-pimelic acid[1] (see p. [illegible]), and can be prepared by oxidation of the corresponding alcohol cyclohexanol. It [illegible] b.p. 155°, with a smell of peppermint. On reduction it yields cyclohexanol, and on oxidation with nitric acid gives adipic acid.

Cyclohexanone is a tautomeric compound and may react either as a ketone or as a hydrogenated phenol (Δ^1-tetrahydrophenol).[2]



As a ketone it unites with hydroxylamine and sodium bisulphite

[1] Numerous other stereoisomeric polymethylene derivatives [illegible] the carboxylic acids. [2] Other examples [illegible] methyl [illegible] J. C. S., 1908, 93, 1033; Perkin and [illegible] naphthalene described on p. [illegible]. [3] Alkyl-keto-hexamethylenes [illegible] manner from alkyl-pimelic acids; Zelinsky and Generosow, Ber. [illegible] 39, [illegible]

and as a phenol it may be acetylated by boiling with acetic anhydride to form the acetyl ester of Δ^1-tetrahydro-phenol, b.p. 180° to 181°.

p-**Diketo-hexamethylene,** *cyclohexane-1 : 4-dione, tetrahydro-quinone,*

$$CO\left\langle\begin{matrix} CH_2-CH_2 \\ CH_2-CH_2 \end{matrix}\right\rangle CO,$$

is obtained from succinylo-succinic ester (p. 460) by hydrolysis and elimination of carbon dioxide. It melts at 78°, and on reduction yields quinitol. *p*-Diketo-hexamethylene forms a dioxime, which in the presence of pyridine reacts with bromine in much the same manner as acetoxime (p. 153) to give *p*-dibromo-dinitroso-hexamethylene, $ON \cdot CBr(CH_2 \cdot CH_2)_2 \cdot CBr \cdot NO$. With chlorine the corresponding chloro-nitroso compound is formed. Both of these halogen derivatives occur in two stereoisomeric forms, as illustrated in the following formulæ:[1]

cis Form *trans* Form

Up to the present few aldehydes of this series are known. **Hexahydro benzaldehyde,** $C_6H_{11} \cdot CHO$, b.p. 159°, is obtained by the oxidation of *hexahydro-benzyl alcohol*, $C_6H_{11} \cdot CH_2OH$. **Hexahydro *m*-toluic aldehyde,** $CH_3 \cdot C_6H_{10} \cdot CHO$, has been prepared by treating ortho-formic ester with methylcyclohexyl magnesium bromide.[2] It is a liquid of strong odour, b.p. 176° to 178°.

Hydro-aromatic carboxylic acids resemble aliphatic acids in their properties. The following compounds of this type may be mentioned.

Hexahydro-benzoic acid, $C_6H_{11} \cdot COOH$, can be obtained by the reduction of benzoic acid, by the action of carbon dioxide on cyclohexyl magnesium iodide,[3] and by a number of other methods. It crystallises in prisms, melts at 30° to 31°, boils at 232°, and has a rancid odour. Numerous homologues of this acid are known, which are probably isomeric with the natural *naphthenic acids* occurring in Caucasian petroleum.

Quinic acid, *tetrahydroxy-hexahydro-benzoic acid*, $(HO)_4C_6H_7 \cdot COOH$, is present in cinchona bark, coffee beans, sugar beet and other sources. The acid prepared from cinchona bark is optically active and melts at 162°. It is also known in an inactive form. On oxidation it is converted into quinone, and when heated with hydriodic acid gives benzoic acid. With benzoyl chloride it yields *dibenzoylhydroquinone*, $C_6H_4(O \cdot COC_6H_5)_2$, m.p. 199°.

The **hydro-phthalic acids** were carefully examined by Baeyer.[4]

[1] Piloty and Steinbock, *Ber.*, 1902, 35, 3101. [2] Tschitschibabin, *Ber.*, 1904, 37, 850. [3] Zelinksy, *Ber.*, 1902, 35, 2687. [4] The results are summarised in *Ber.*, 1890, 23, 1272, and *Ann.*, 1892, 269, 176.

in an attempt to determine the constitution of benzene. Although unsuccessful in this respect, these arduous investigations brought to light the existence of a number of isomerides, since both structural isomerism and stereoisomerism may occur among these compounds.

Thus the reduction of phthalic acid has led to the isolation of eleven different *dihydro-phthalic acids*, $C_6H_6(COOH)_2$, four *tetrahydro-phthalic acids*, $C_6H_8(COOH)_2$, and two *hexahydro-phthalic acids*, $C_6H_{10}(COOH)_2$. Several hydro-derivatives of terephthalic and isophthalic acids are also known. We are dealing here with the same type of geometrical isomerism as was outlined in connection with quinitol (p. 461), i.e. *cis-trans* isomerism. In their interconversions the isomerides recall the behaviour of ethylene derivatives, as is seen in the case of the hexahydro-phthalic acids:

cis Hexahydro phthalic acid (m.p. 192°)	$\xrightarrow{\text{with HCl}}$	*trans* Hexahydro phthalic acid (m.p. 215°)
$\downarrow\uparrow$		$\downarrow\uparrow$
cis Anhydride (m.p. 32°)	$\xleftarrow{\text{on heating}}$	*trans* Anhydride (m.p. 140°)

II.—TERPENES AND CAMPHORS[1]

Terpenes are cyclic hydrocarbons of the formula $(C_5H_8)_n$, and occur widely distributed in nature. They are the chief constituents of the "essential oils" obtained by distilling with steam the sap and tissues of certain plants—particularly those of the coniferous and citrus families. Essential oils or ethereal oils prepared in this way are used in the production of perfumes and in pharmacy. Accompanying the terpenes are also found oxygen derivatives of the terpenes (alcohols and ketones), which are classed under the name of *camphors*, and certain closely related open-chain alcohols and aldehydes known as *olefinic terpenes* (*cf.* p. 145). Terpenes and essential oils have been the subject of many careful and elaborate investigations from 1884 onwards, more especially at the hands of O. Wallach. Even at the present time, however, the constitution of comparatively few of the terpenes has been established with certainty.

Hydrocarbons of this group are generally subdivided into *hemiterpenes*, C_5H_8 (see Isoprene, p. 115), *terpenes*, $C_{10}H_{16}$, *sesquiterpenes*, $C_{15}H_{24}$, and *diterpenes*. The different classes are readily distinguished by the marked differences in boiling-point.

The terpenes, $C_{10}H_{16}$, are all unsaturated hydrocarbons containing

[1] Compare O. Wallach, *Terpene und Campher* (Leipzig, 1909); *Natural Terpenes*, J. W. Baker (Methuen, 1930); *The Terpenes*, J. L. Simonsen (Camb. Univ. Press, 1931).

either one or two ethylene bonds in the molecule, according to which they are again divided as follows —

1 **Monocyclic terpenes**, containing two double bonds These are dihydro-cymenes, and may therefore be regarded as partially reduced benzene derivatives Included in this class are limonene (dipentene), sylvestrene, terpinene and terpinolene Owing to the presence of two double bonds they are capable of adding on two or four monovalent atoms or groups

2 **Dicyclic terpenes**, containing one double bond in the molecule These are built up of two ring systems, *e g* a combination of a hexamethylene with a tetramethylene ring Compounds of this type are pinene, camphene and fenchene, each of which can unite with two monovalent atoms or groups

Camphors and other terpene derivatives can be classified in a similar manner

According to recent work,[1] the **sesquiterpenes** are related to naphthalene in the same way as the terpenes to benzene Comparatively little is known of the chemistry of this group

Of the above compounds only the terpenes proper can be treated with any detail in these pages

Properties and Chemical Behaviour —Camphene is a solid at ordinary temperatures, but with this exception, the terpenes are colourless, strongly-refracting liquids, which boil between 150° and 180°, are insoluble in water and volatilise readily with steam. They are characterised by a pleasant smell, and many of them are optically active

Their nature as unsaturated compounds is shown by their addition reactions and tendency to polymerise They unite with chlorine, bromine,[2] and hydrogen halides to form halogen-substituted compounds, which are of interest as being intermediate products in the transformation of terpenes into terpene alcohols Further, many terpenes add on N_2O_3, N_2O_4, NOCl and NOBr to yield nitrosites, nitrosates, nitroso-chlorides and nitroso-bromides (see p 110)

A number of the terpenes are labile, readily isomerising under the influence of acids, for example, into a more stable form

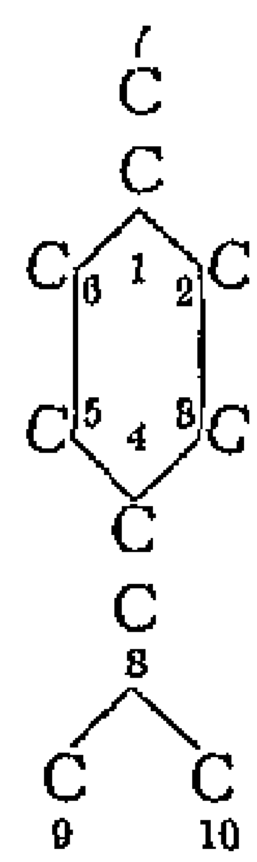
Another point of interest is the behaviour of the terpenes on oxidation In many cases this is effected even by atmospheric oxygen, with the production of resins The action of mild oxidising agents (iodine, dilute nitric acid) frequently leads to the formation of benzene derivatives, or breaks down the terpenes to known aliphatic compounds This process is often used in determining their structure Energetic oxidising agents, such as concentrated nitric acid, generally produce complete resinification

[1] See Ruzicka and co-workers, *Helv Chim Acta*, 1921, 4, 505, 1922, 5, 315, 369, 1924, 7, 84

[2] Baeyer and Villiger have made use of exhaustive bromination as a means of determining the structure of the carbon framework of many terpenes

Monocyclic Terpenes and Camphors

Nomenclature.—The majority of the monocyclic terpenes are derived from *p*-cymene, and a few from *m*-cymene. Following a suggestion of Baeyer, the structure of these compounds is expressed by reference to the saturated parent hydrocarbon, *e.g.* hexahydro-cymene, the carbon atoms of which are numbered as in the annexed formula. The position of the double bond is indicated in the usual way (see p. 459), a double bond between the atoms 2 and 3 being shown by Δ^2.

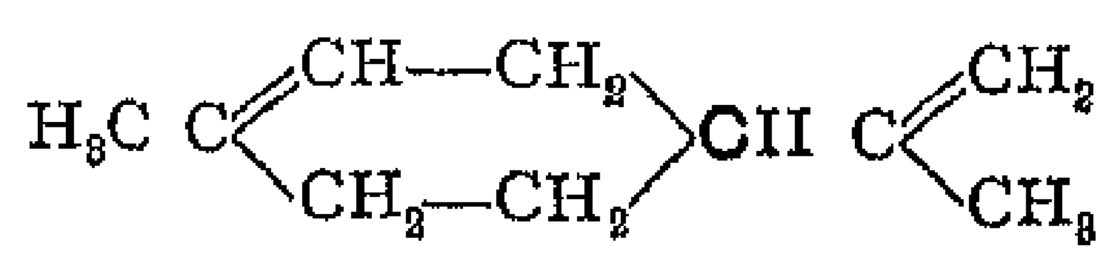


Hexahydro-cymene, $C_{10}H_{20}$, commonly known as *menthane*, is not found in nature but may be prepared by reducing *p*-cymene with hydrogen and finely-divided nickel. It boils at 170°.

Tetrahydro-cymenes are therefore described as *menthenes*, and dihydro-cymenes as *menthadienes*.

Terpenes

Limonene, $\Delta^{1,8}$-*menthadiene*,


(?)

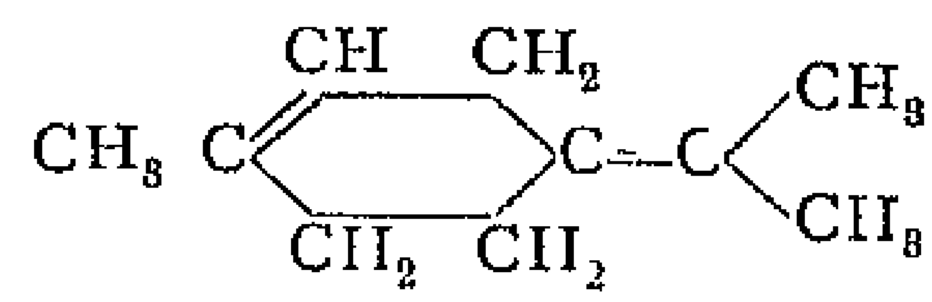
exists in dextro-, lævo- and inactive forms, as would be expected from the presence of an asymmetric atom in the molecule.[1]

d-**Limonene**, also known as carvene, citrene or hesperidene, is the chief constituent of the oil of orange rind, dill oil and oil of cumin. It occurs together with pinene in oil of lemons. *l*-**Limonene** is found with *l*-pinene in pine-needle oil; it may be prepared from carvone or from perillaldehyde.[2] Both forms of limonene are liquids of boiling-point 175°, with a strong smell of lemons. They yield crystalline tetrabromides, $C_{10}H_{16}Br_4$, m.p. 104° to 105°, which are also distinguished by rotations of opposite sign. Both limonenes unite with nitrosyl chloride,[3] each forming two compounds differing in specific rotation. On treatment with alkali these part with hydrochloric acid and are transformed into the oxime of carvone.

i-**Limonene, dipentene**, *cinene*, is produced by mixing equal amounts of *d*- and *l*-limonenes, and is found associated with cineol, $C_{10}H_{18}O$, in oleum cinae. It is formed by the elimination of water from terpineol, and from pinene and camphene by heating at 250° to 270°. It smells of lemons, boils at 175°, and its tetrabromide melts at 124°. Among its derivatives are terpineol, $C_{10}H_{17}OH$, terpin, $C_{10}H_{18}(OH)_2$, and cineol, $C_{10}H_{18}O$.

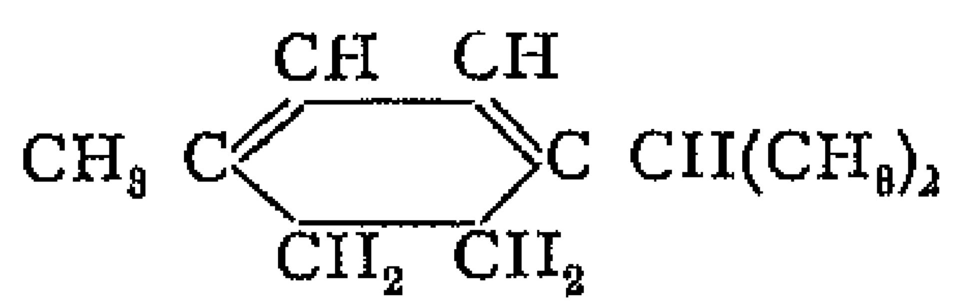
[1] For the constitution see F. W. Semmler, *Ber.*, 1900, 33, 1457. [2] Semmler and Zaar, *Ber.*, 1911, 44, 52. [3] Tilden and Shenstone, *J. C. S.*, 1875, 13, 514.

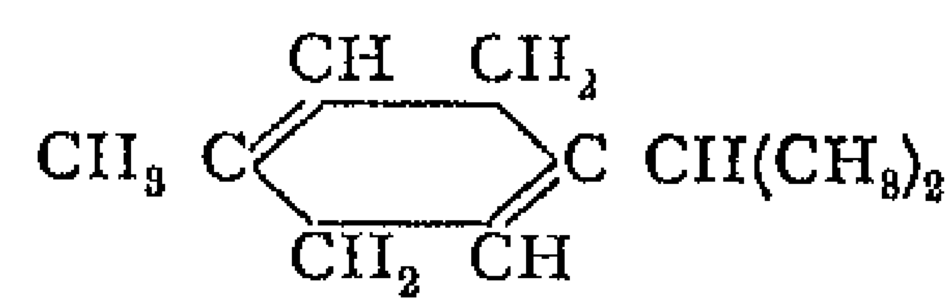
Terpinolene, $\Delta^{1,4(8)}$-*menthadiene*,



is obtained when terpineol (p 469) is heated for a short time with oxalic acid solution. It boils at 183° to 185°, and on further treatment with acids readily yields terpinene.

Terpinene, $\Delta^{1,3}$-*dihydro-cymene* and $\Delta^{1,4}$-*dihydro-cymene*,[1]





is present in cardamom oil and is optically inactive. It smells like cymene and boils at 179° to 181°. Terpinene is formed when dipentene or phellandrene is boiled with dilute sulphuric acid, and is distinguished by its stability towards mineral acids. Hence it is also obtained when terpin hydrate, cineol, terpineol or dihydro-carveol are heated with dilute sulphuric acid. Terpinene is conveniently prepared by shaking pinene (oil of turpentine) with concentrated sulphuric acid. It forms a nitrosite of melting-point 155°, but does not give definite addition products with bromine or hydrogen halides. Ordinary terpinene consists mainly of $\Delta^{1,3}$-dihydro-cymene and contains also some $\Delta^{1,4}$-dihydro-cymene.

Sylvestrene,[2] $C_{10}H_{16}$, b p 176°, is the limonene of the *m*-cymene series, and has been prepared from Swedish and Russian turpentines. Simonsen and Rao have shown that it does not occur naturally in these sources but is formed from the carene present by secondary changes due to the treatment of the oils with hydrogen chloride (see p 473).

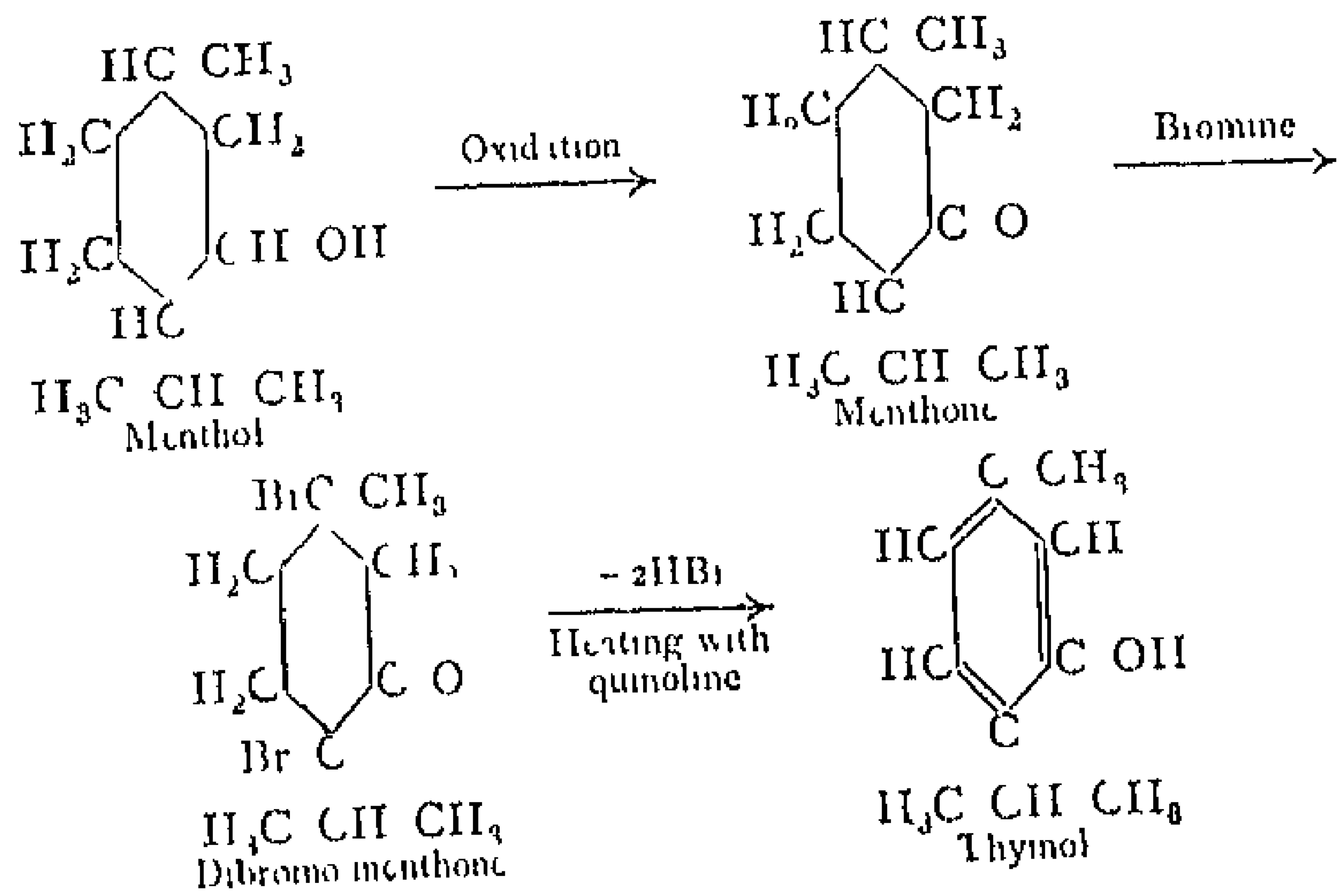
Phellandrene, $C_{10}H_{16}$, was first isolated from water-fennel (*Phellandrium aquaticum*) from which it takes its name. It also occurs in other ethereal oils and exists in *d*- and *l*-forms, neither of which has yet been obtained in the pure state. With acids it very readily undergoes change.

Alcohols and Ketones

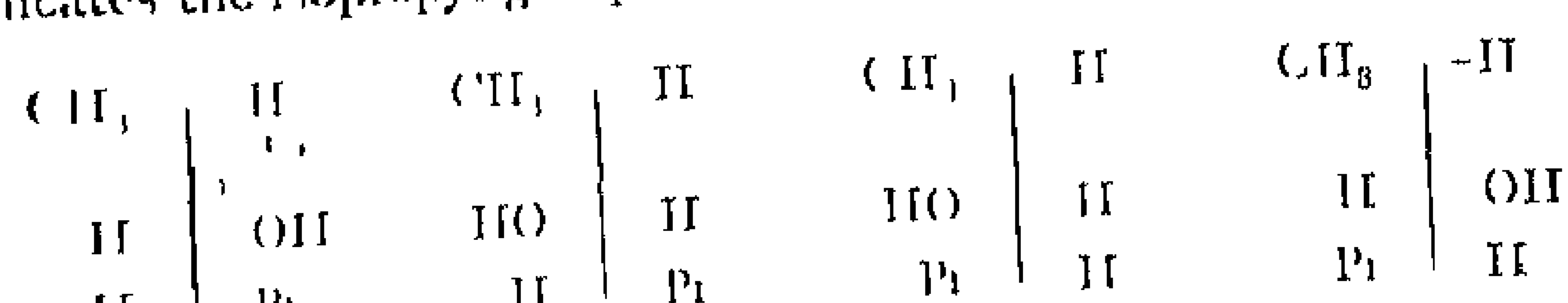
Menthol, 3-*menthanol*, is the odorous and chief constituent of oil of peppermint, from which it may be separated in the solid state by cooling. It melts at 43°, boils at 213° and is employed as an antiseptic

[1] Harries and Majima, *Ber.*, 1908, 41, 2516. Wallach, *Ann.*, 1908, 362, 293. Semmler, *Ber.*, 1908, 41, 4474. F. Richter and Wolff, *Ber.*, 1927, 60, 477. [2] For synthesis see Perkin, *Proc. Chem. Soc.*, 1910, 26, 97.

and anæsthetic. On reduction it yields hexahydro-cymene. When oxidised it is converted into the corresponding ketone, **menthone**, b.p. 207°, which also occurs in oil of peppermint and other essential oils. The constitution of menthol and menthone is shown by the conversion of the latter into thymol as follows:[1]



Owing to the rigidity of the cyclohexane ring, the three asymmetric atoms in menthol are not free to rotate around the bonds joining them. Various geometrically isomeric forms are therefore possible. The relative configurations of these compounds have largely been established by Read and his co-workers (see p. 470). In the following formulæ Pr indicates the isopropyl group.

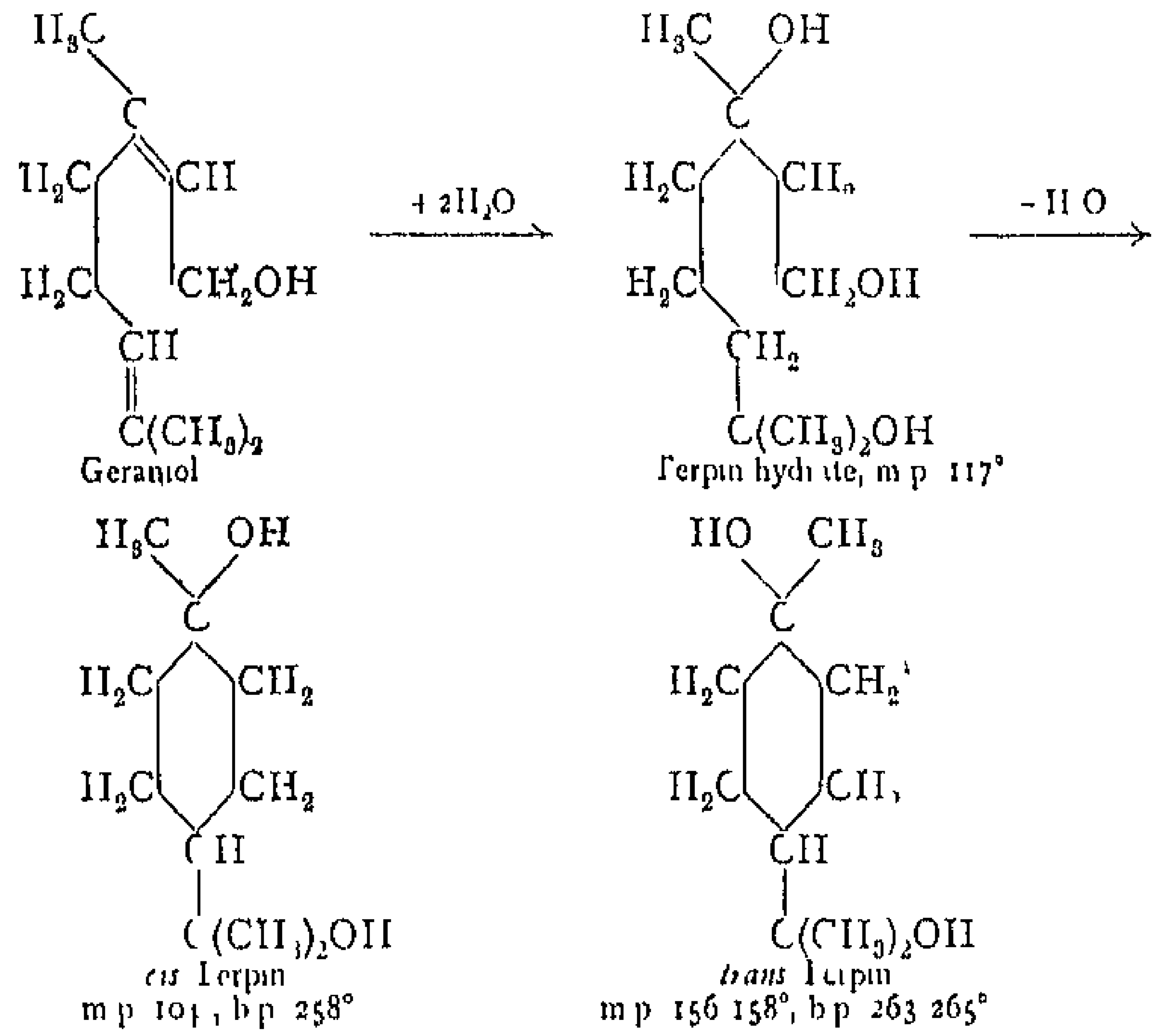


l (or *d*)-Menthol, m.p. 43° — *d* (or *l*) *neo* Menthol, an oil — *d* (or *l*) *iso* Menthol, m.p. 81° — *neoiso* Menthols

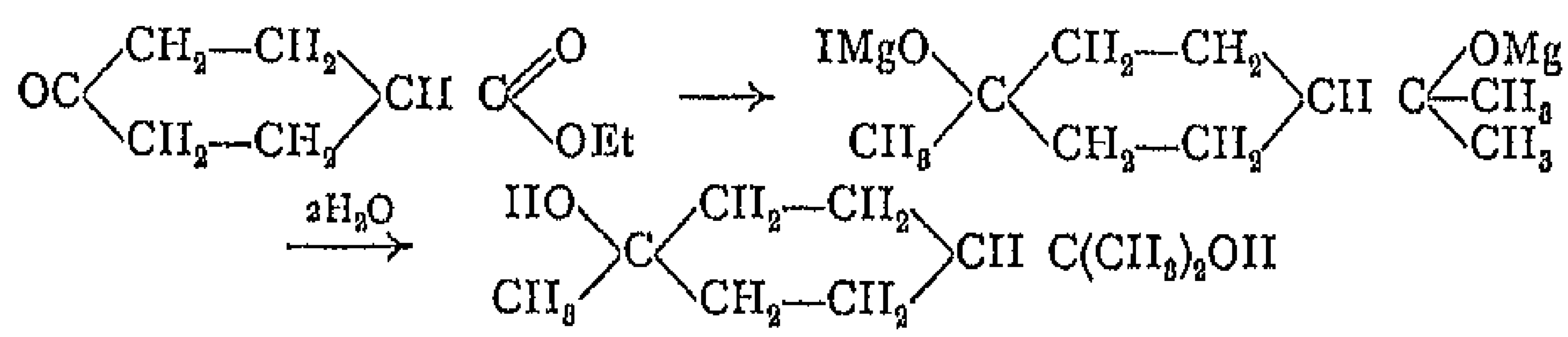
Terpin, 1 : 8-*menthane-diol*, $C_{10}H_{20}O_2$, exists in two stereoisomeric (*cis*- and *trans*-) forms. A crystalline hydrate of terpin, known as *terpin hydrate*, is produced when pinene or dipentene is allowed to stand for some time at the ordinary temperature in contact with dilute mineral acids. Terpin hydrate is also formed from geraniol by treat-

[1] Beckmann and Eickelberg, *Ber.*, 1896, 29, 418; also Jünger and Klages, *Ber.*, 1896, 29, 314. For syntheses of menthol see Perkin, jun., *Proc. Chem. Soc.*, 1905, 21, 255; Kötz and Hesse, *Ann.*, 1905, 342, 306. For a synthesis of optically active menthone see Kötz and Schwarz, *Ann.*, 1907, 357, 209.

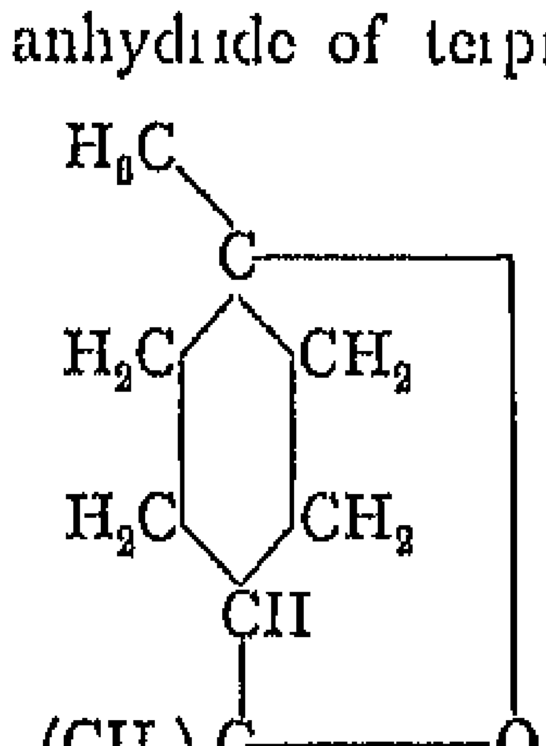
ment with dilute sulphuric acid. On prolonged heating at 100° it yields *cis*-terpin.



Perkin and Kay[1] have synthesised terpin by treating cyclohexanone-4 carboxylic ester with excess of methyl magnesium iodide, and have thus confirmed its constitution.



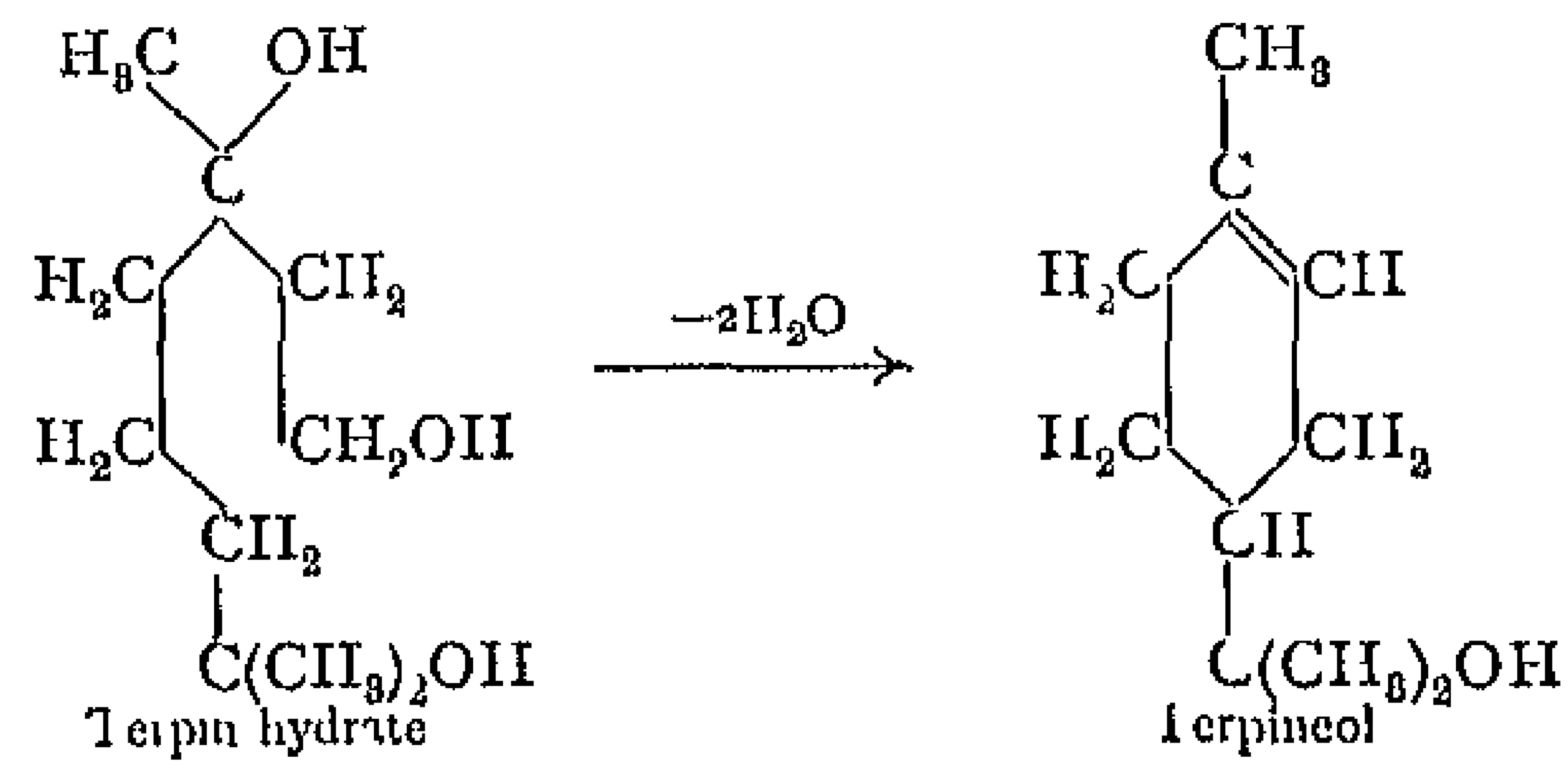
Cineol, of the annexed formula, is an inner anhydride of terpin, and occurs in many ethereal oils, such as oil of eucalyptus, wormseed oil and rosemary oil. It is a liquid of boiling-point 176°, with a smell of camphor. When treated with hydrochloric acid in glacial acetic acid solution, it is converted into dipentene dihydrochloride, $C_{10}H_{18}Cl_2$.


Cineol

Terpineol, Δ^1-*menthen-8-ol*, is a solid, m.p. 35°, and b.p. 219°. It is obtained from terpin hydrate by treating it under certain conditions

[1] *J. C. S.*, 1907, 91, 372.

with dilute sulphuric acid, when two molecules of water are removed as follows —



Terpineol[1] is present in a number of essential oils and has an odour of lilac. Hence it is used in the manufacture of perfumes. When heated with potassium bisulphate it yields dipentene, and with oxalic acid, terpinolene. Carvacrol and carvone (see below) may be prepared from the nitrosochloride of terpineol.

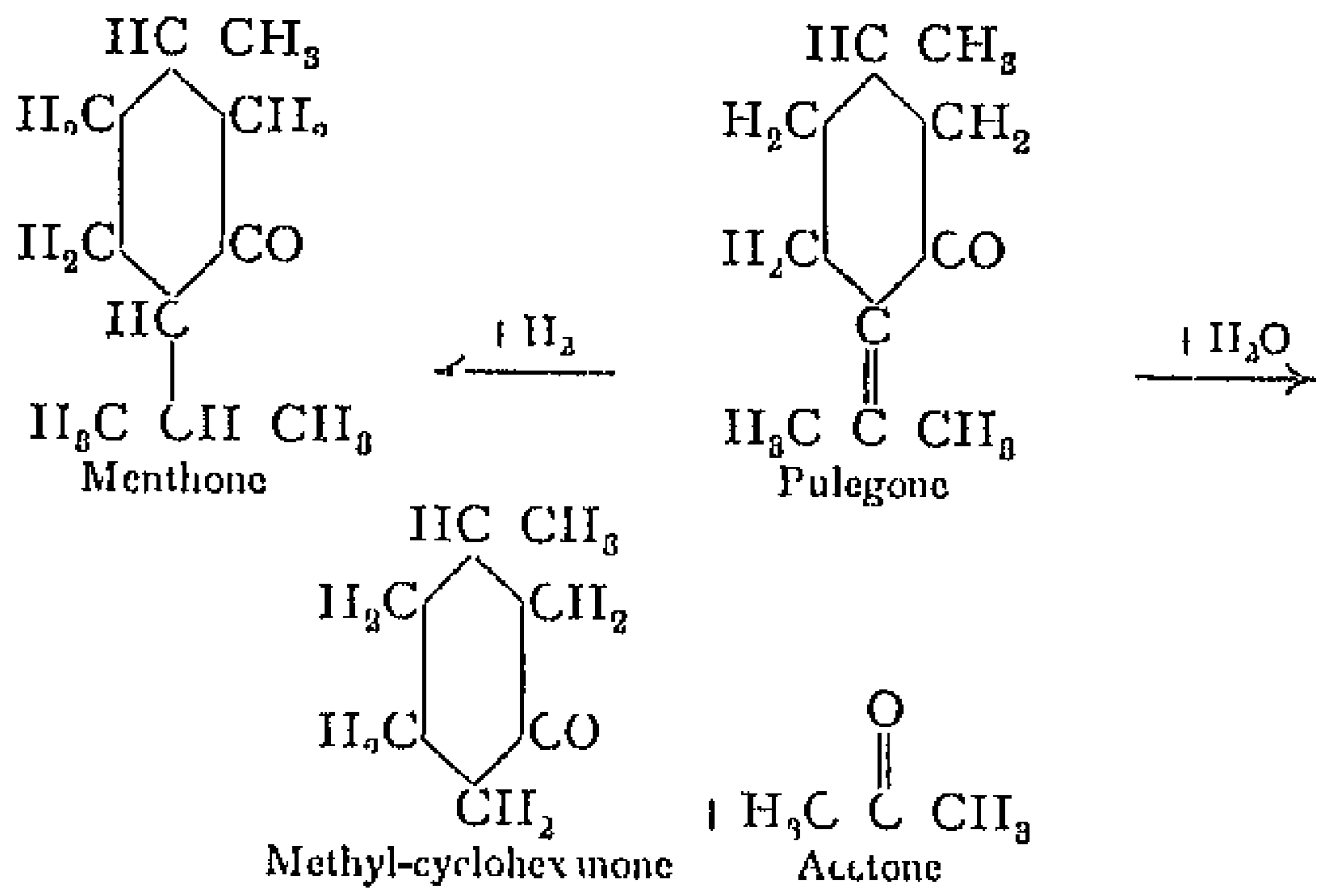
Among the ketones of this group are **menthone**, already described on p. 468, piperitone, pulegone and carvone. Buchu-camphor is an example of a ketonic alcohol.

Piperitone, Δ^1-*menthen-3-one*, is an unsaturated ketone found in the *l*-form in a number of eucalyptus oils (H. G. Smith), especially in that of the Broad-leaved Peppermint (*E. Dives*). More recently a *d*-piperitone has been isolated by Simonsen from the essential oil of a Himalayan grass, *Andropogon Jwarancusa*. Piperitone has been carefully investigated by Read and his co-workers and in his hands has proved of great value in establishing the configurations of the menthones, menthols and menthylamines.[2] On hydrogenation it yields a mixture of menthone and isomenthone.

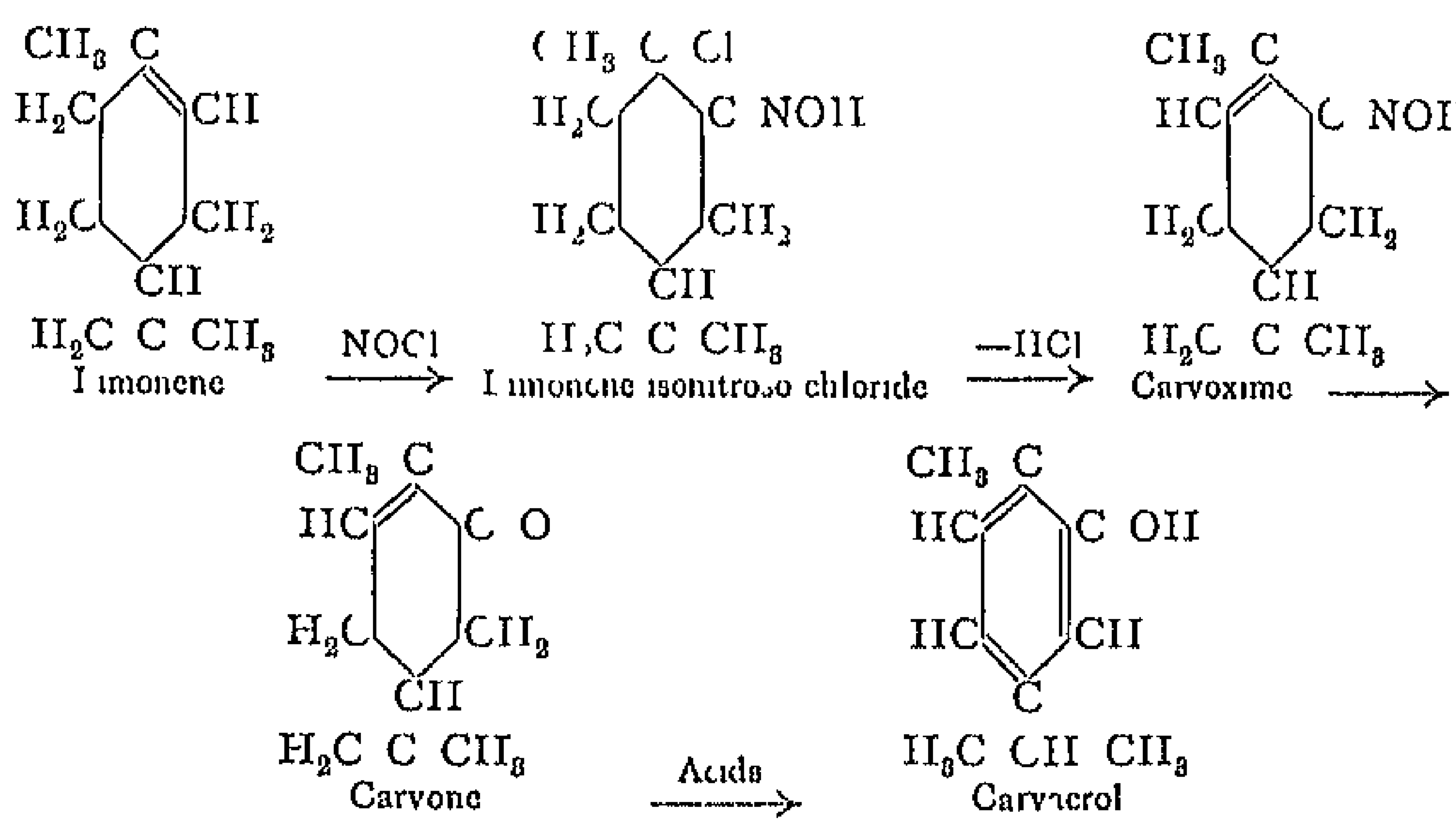
Pulegone, $\Delta^{4(8)}$ *menthen-3-one*, b.p. 221°, is present in oil of pennyroyal. The keto-group occupies a similar position to that in menthone, into which compound pulegone may be converted by hydrogenation. When superheated with formic acid or water, pulegone is hydrolysed to 3-methyl-cyclohexanone and acetone, from which its constitution is deduced.[3] On the other hand, by the condensation of methyl-cyclohexanone with acetone, an isomeride of pulegone is obtained.[4]

Pulegone reacts with hydroxylamine in the normal manner to form an oxime; it also yields an addition product in which hydroxylamine is attached to the unsaturated linking, the group C=C being converted into CH—C.NHOH.

[1] For synthesis see Perkin, *J. C. S.*, 1904, 85, 654; 1908, 93, 1871. [2] For a summary, see J. Read, *J. S. C. I.*, 1927, 46, *Chem. and Ind.*, p. 871, where a detailed bibliography will be found. [3] Wallach, *Ber.*, 1899, 32, 3338. [4] Wallach, *Ann.*, 1898, 300, 267.



Carvone, $\Delta^{6,8}$-*menthadiene-2-one*, formerly known as carvol, exists like limonene in *d*-, *l*- and *i*-modifications. *d*-Carvone is the odorous and chief constituent of caraway oil. It melts at 62°, and boils at 230° under 755 mm. and at 91° under 5 to 6 mm. It readily isomerises into carvacrol, the hydroxyl group of which has been shown to occupy the 2-position. This must also be the position of the carbonyl group of carvone. The double bond may be located from the close relationship existing between carvone and limonene, and has been established with certainty by the degradation of carvone.

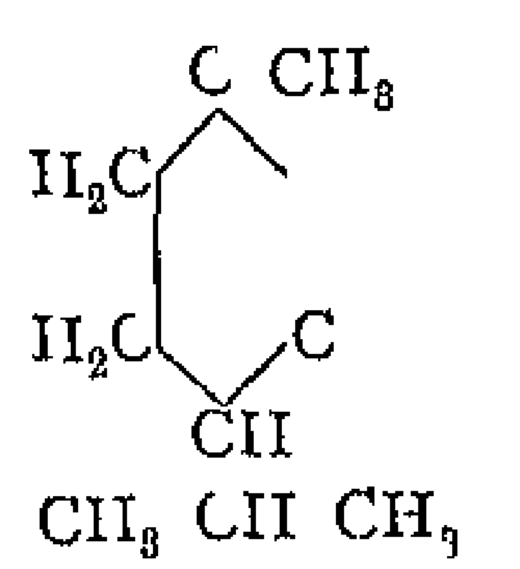
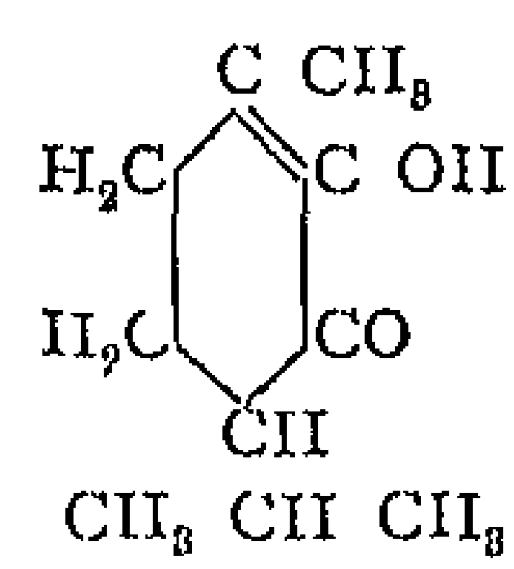


Carvone on reduction gives dihydro-carveol, and finally tetrahydro-carveol or *carvomenthol*.

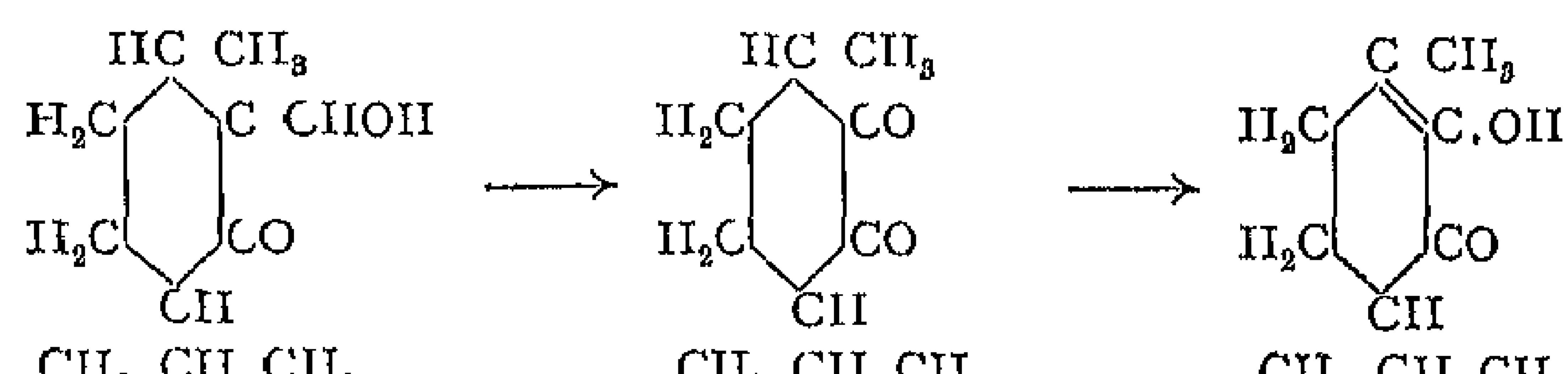
Under the influence of strong aqueous acids carvone adds on the elements of water to the double bond in the side chain to form a

carvone hydrate (hydroxy dihydrocarvone). At the same time part of the carvone is converted into carvacrol.

Buchu-camphor, *diosphenol*, Δ^1-*menthen-2-ol-3-one*, $C_{10}H_{16}O_2$, is prepared from an essential oil obtained from various kinds of the genus *Barosma* found in South Africa. It boils at 109° to 110° under 10 mm pressure, and melts at 83° to 84°. The constitution of this substance has been established by Semmler and McKenzie.[1] One of the two oxygen atoms is contained in an alcoholic hydroxyl group, since the compound yields an acetate and a benzoate. The second is a ketonic oxygen atom, as Buchu-camphor forms a normal oxime. Hence the substance is a ketonic alcohol and has also been shown to be monocyclic and unsaturated. Oxidation with ozone leads to the production of α-isopropyl-γ-acetyl-n-butyric acid, thus proving the structure of that part of the molecule shown in I below. The arrangement of the remaining atoms is deduced from the reduction of Buchu-camphor to the glycol, $C_{10}H_{20}O_2$, which on oxidation yields α-isopropyl-α^1-methyladipic acid, thus showing the presence of a six-membered ring with methyl and isopropyl groups in the para-position to one another. The disposition of the ketonic and hydroxyl groups is now obvious. Further, it follows that the double bond must be attached to the carbon atom linked to the methyl group, the position 2 : 3 being impossible. Buchu camphor therefore possesses the structure II.

I  II 

The *synthesis of Buchu-camphor* has been effected by Semmler and McKenzie (*loc. cit.*), starting with hydroxymethylene-menthone and oxidising this to the diketone, $C_{10}H_{16}O_2$. The latter may then be transformed in various ways, *e.g.* with acids or alkalis, into Buchu-camphor.

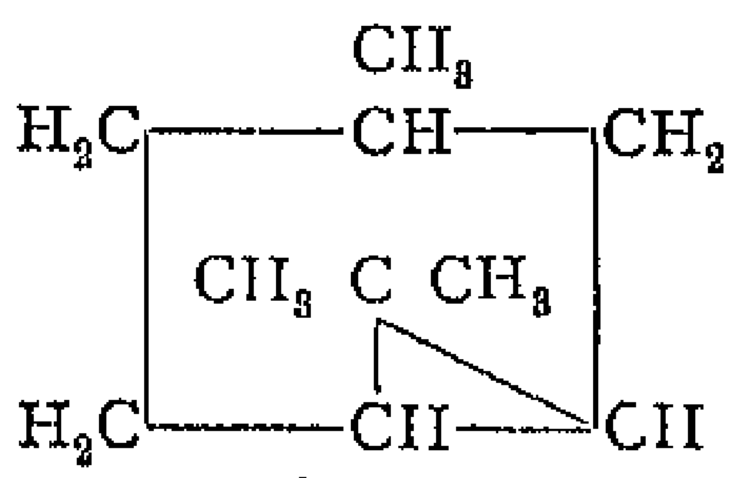


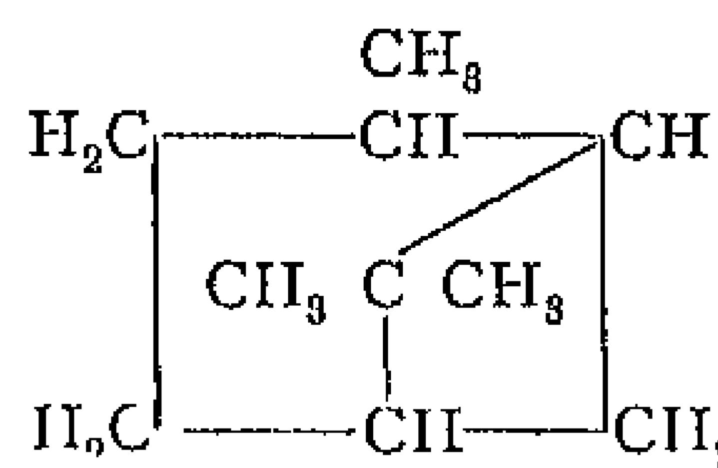
Hydroxymethylene menthone — Diketone — Buchu camphor or diosphenol

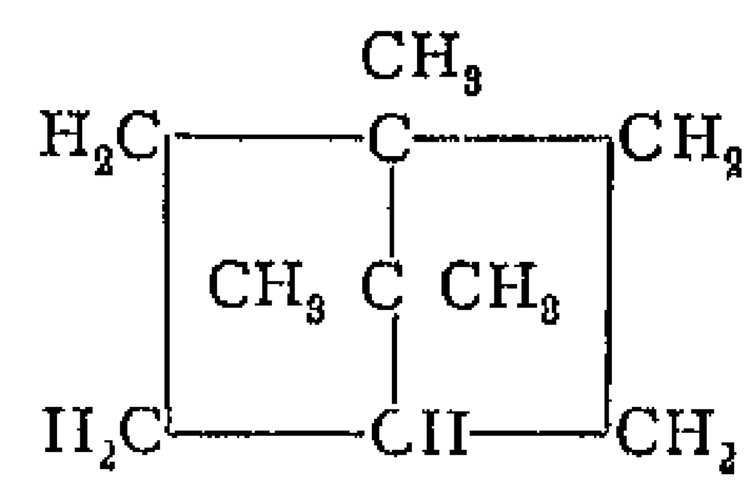
[1] *Ber.*, 1906, 39, 1158. See also Wallach and Weissenborn, *Ann.*, 1924, 437, 148.

Dicyclic Terpenes and Camphors

The most important member of this class is ordinary or Japanese camphor. Before discussing this compound in detail, however, the parent hydrocarbons of the alcohols and ketones will be considered. Just as many of the monocyclic terpenes may be traced back to the saturated hydrocarbon menthane, the dicyclic terpenes and their derivatives may be referred, according to the type of "bridged-ring" present, to one of the three saturated hydrocarbons, carane, pinane and camphane.

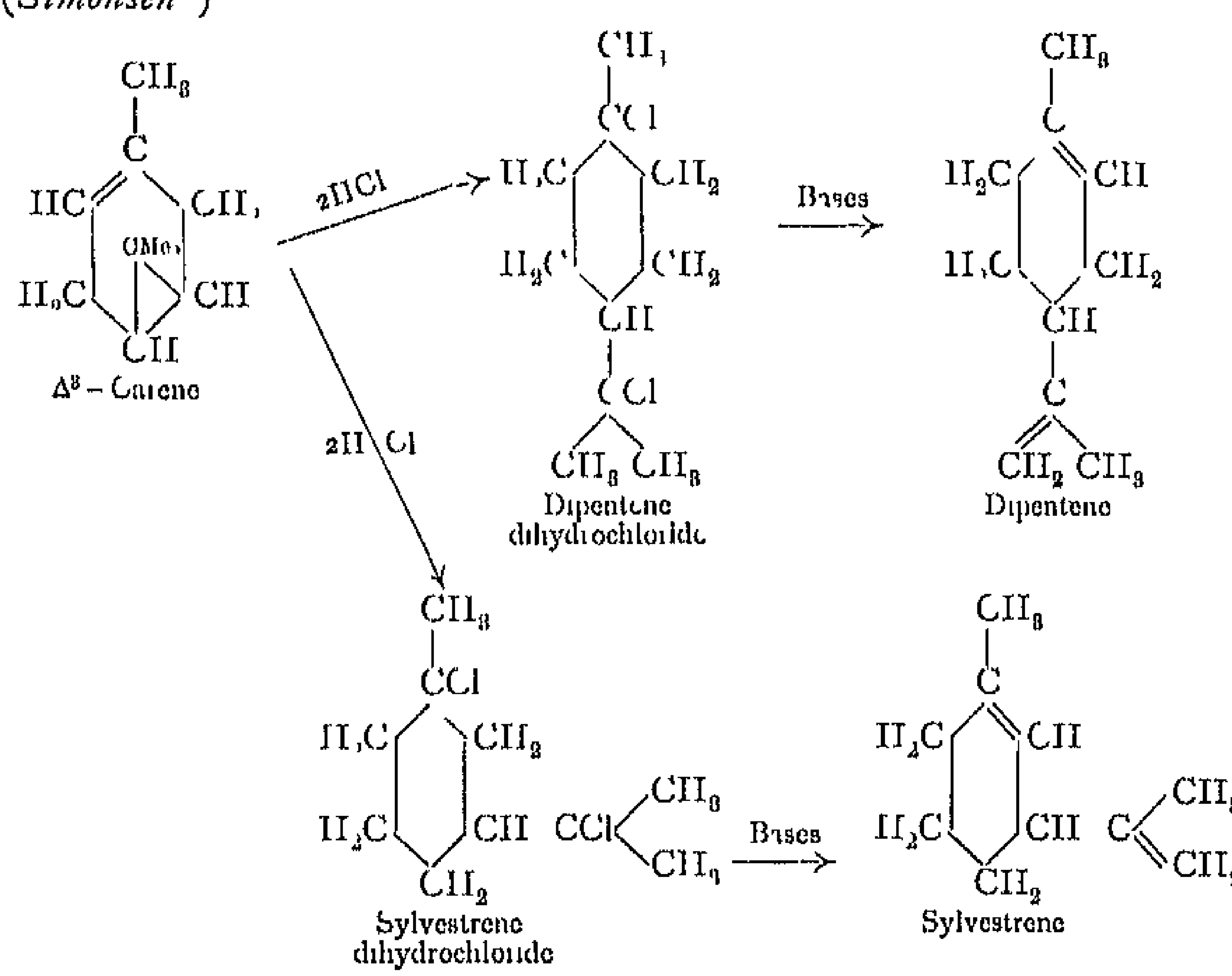

Carane


Pinane


Camphane

Dicyclic Terpenes

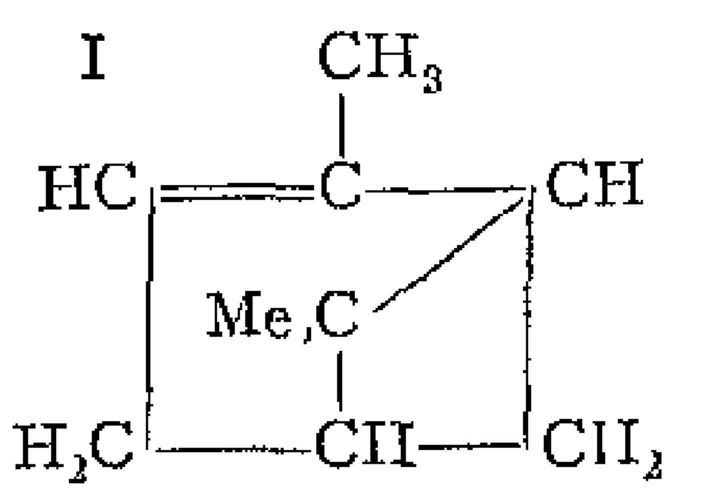
Carenes probably occur more widely in nature than was formerly supposed, but during the purification of the essential oils with hydrogen chloride they become transformed into dipentene hydrochloride and sylvestrene dihydrochloride by the opening of the cyclopropane ring (*Simonsen*[1]).



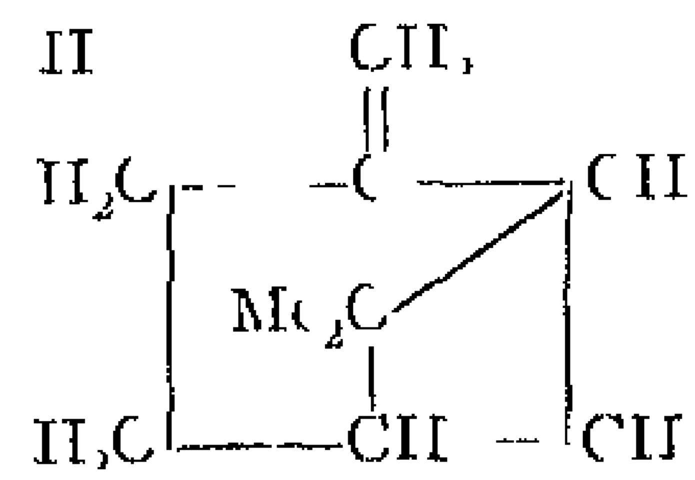
[1] B. S. Rao and J. L. Simonsen, *J. C. S.*, 1922, 121, 2294; 1925, 127, 2494

α-Pinene (I) is a common constituent of many ethereal oils, and is especially abundant in the *turpentine oils*[1] obtained by distilling the resinous exudations of pines and firs. Associated with it is found an isomeride, **β-pinene** or **nopinene** (II). Although these compounds differ in the position of the double bond, it is not possible to distinguish between them by means of simple addition reactions, because in many cases they yield the same products. With hydrogen chloride, for example, each pinene gives the hydrochloride (III), and in the presence of dilute sulphuric acid each is converted into the same terpin. Indication of a difference in structure is furnished by their behaviour on oxidation with potassium permanganate, when α-pinene yields *pinonic acid* and nopinene gives *nopinic acid*. Under certain conditions α-pinene is oxidised much more readily than nopinene by mercuric acetate. β-Pinene also forms mercury addition compounds which are readily isolated.[2]

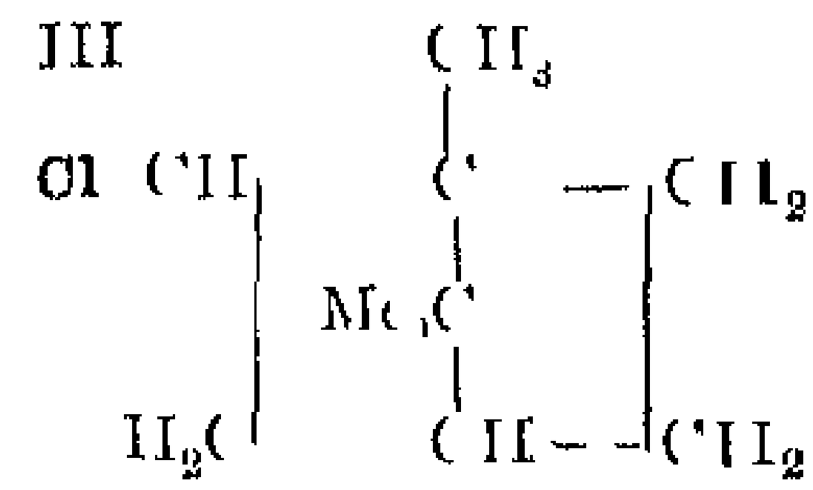
I



II



III



Pinene combines with two atoms of chlorine or bromine to form compounds which on heating break up into hydrogen halide and *p*-cymene. When dry hydrochloric acid gas is led into well cooled pinene, the pinene hydrochloride first formed isomerises with great rapidity into *bornyl chloride* (III), which separates out as a crystalline mass of melting-point 131° to 132°. Owing to its close resemblance to camphor in smell and appearance, this substance is sometimes known as "artificial camphor." In its formation not only has addition of hydrochloric acid taken place, but the "pinane bridge" has simultaneously been changed into the "camphane bridge."

This is confirmed by the fact that when the magnesium compound of the hydrochloride is treated with oxygen, and the resulting

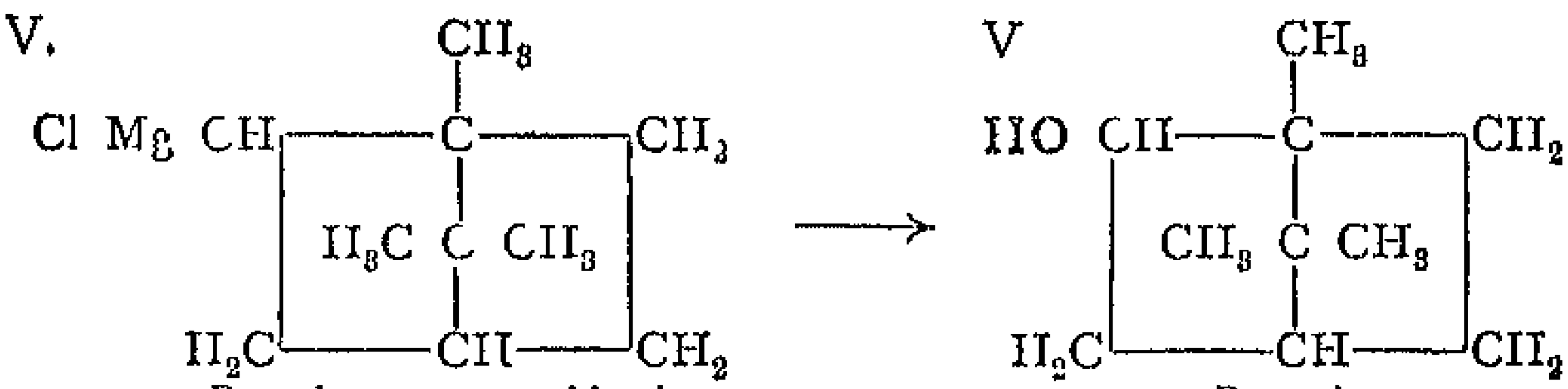
[1] Turpentine resin exudes in considerable quantities from firs, pines and other conifers when incisions are made in the bark of the tree. By distillation in steam the resin is separated into volatile turpentine oil and non-volatile colophonium (*rosin*). Turpentine oil of commerce is a colourless liquid of sp. gr. 0·85 to 0·91 and is not a homogeneous product, it boils over a range of about 155° to 165°. The oils obtained from different countries—French, Russian, American, Venetian, etc.—show varying optical rotatory power. American oil of turpentine is usually of $[\alpha]_D = +14°$, whereas the French oil is of −30 to −40°. Turpentine is an excellent solvent for resins and is largely used in the preparation of varnishes and lacquers. The United States produces yearly immense quantities of turpentine and rosin. Oil of turpentine absorbs oxygen in air, becoming thick and finally resinifying: the absorbed oxygen is thereby activated (Engler and Weissberg, *Ber.*, 1898, **31**, 3046).

Rosin consists of various modifications of the *anhydrides of sylvic acid* (*abietic acid*, $C_{20}H_{30}O_2$) and is extensively employed in the manufacture of varnishes, rosin soaps, rosin oils, and for sizing paper, etc.

[2] J. Gasopoulos, *Ber.*, 1926, **59**, 2184.

product, $C_{10}H_{17}OMgCl$, decomposed with dilute acids, an almost theoretical yield of borneol (see V) is obtained[1]

IV. V



Bornyl magnesium chloride Borneol

The presence of a tetramethylene ring in pinene is supported by the constitution of its oxidation products, pinonic acid and pinic acid, as well as by its synthesis[2] When heated, pinene yields dipentene (together with isoprene, etc) Other changes are shown in the table on p 483

Pinene exists in one optically inactive and two active forms *d*-Pinene can be isolated by the fractional distillation of American oil of turpentine, and *l*-pinene from French turpentine Inactive pinene is obtained by the action of aniline on active pinene nitroso chloride, m p 103° (obtained from nitrosyl chloride and pinene),[3] when the nitrosyl chloride is again removed

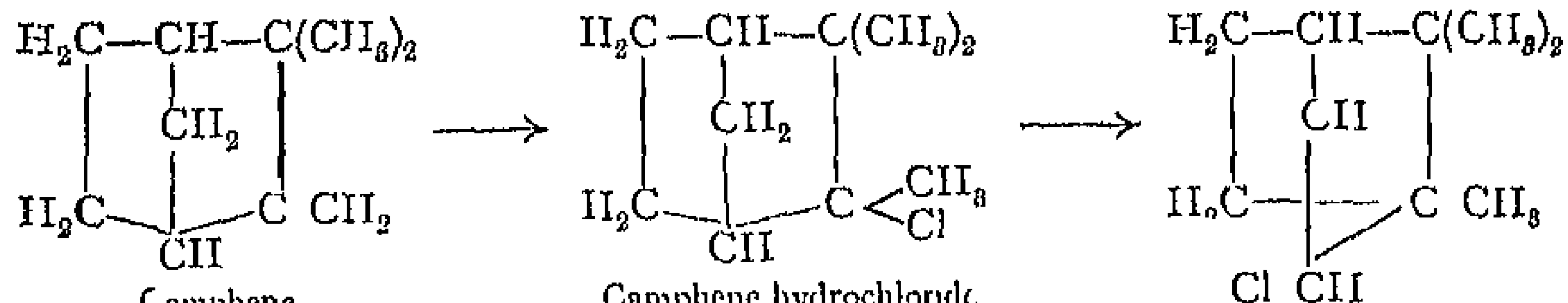
Camphene, $C_{10}H_{16}$, is a solid terpene found as the *d*-form in ginger, rosemary and spike oils, and as the *l*-form in citronella and valerian oils It is produced from bornyl chloride by removing hydrogen chloride with sodium acetate and glacial acetic acid at 200°, or by warming with aniline The constitution of camphene has given rise to much discussion, but may now be regarded as settled in accordance with formula VI

Camphene is a solid, melting at about 50°, with a smell of turpentine and camphor When oxidised with chromic acid it yields camphor If hydrogen chloride is passed into an ethereal solution of camphene there is formed *camphene hydrochloride* (VII), m p 125° to 127° This very readily isomerises into *isobornyl chloride*[4] (VIII or VIII*a*), m p 161° The latter is structurally identical with the bornyl chloride obtained from pinene, and the difference between them can only be explained on the basis of stereoisomerism due to the position (*cis* or *trans*) assumed by the chlorine atom with respect to the $(CH_3)C<$ bridge (see VIII*a* and IX[5]) Recently it has been shown that camphene hydrochloride, isobornyl chloride and bornyl chloride exist in a state of equilibrium with one another, when in the fused state or in solution[6]

[1] A Hesse, *Ber*, 1906, 39, 1127 J Houben, *Ber*, 1905, 38, 3801, 39, 1700 [2] Ruzicka and Trebler, *Helv Chim Acta*, 1921, 4, 666 [3] In the preparation of pinene nitroso chloride, a product of higher melting-point is obtained when alcoholic hydrochloric acid is used in place of concentrated aqueous acid Ruzicka and Trebler, *Helv Chim Acta*, 1920, 3, 756 [4] Meerwein and van Emster, *Ber*, 1920, 53, 1821 [5] Formula VIII*a* is identical with VIII [6] Meerwein and van Emster, *Ber*, 1922, 55, 2500

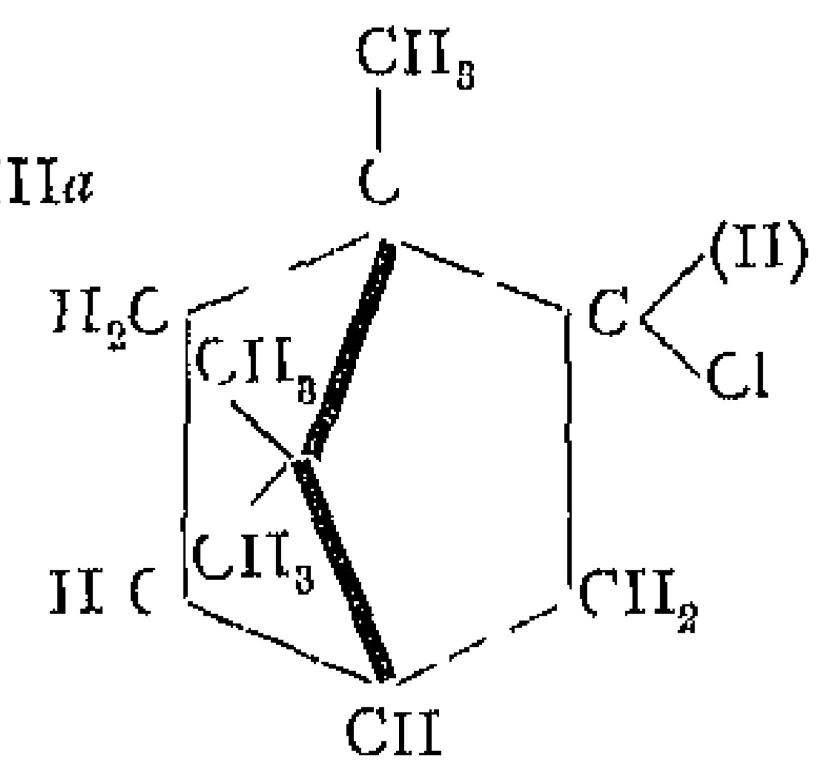
Corresponding to bornyl and isobornyl chlorides are the two stereoisomeric secondary alcohols *borneol* (formula V, p 475) and *isoborneol* Borneol can be obtained in considerable proportion from *both* of the above chlorides by way of the magnesium compounds, but camphene hydrochloride yields a larger proportion of isoborneol [1]

VI VII VIII



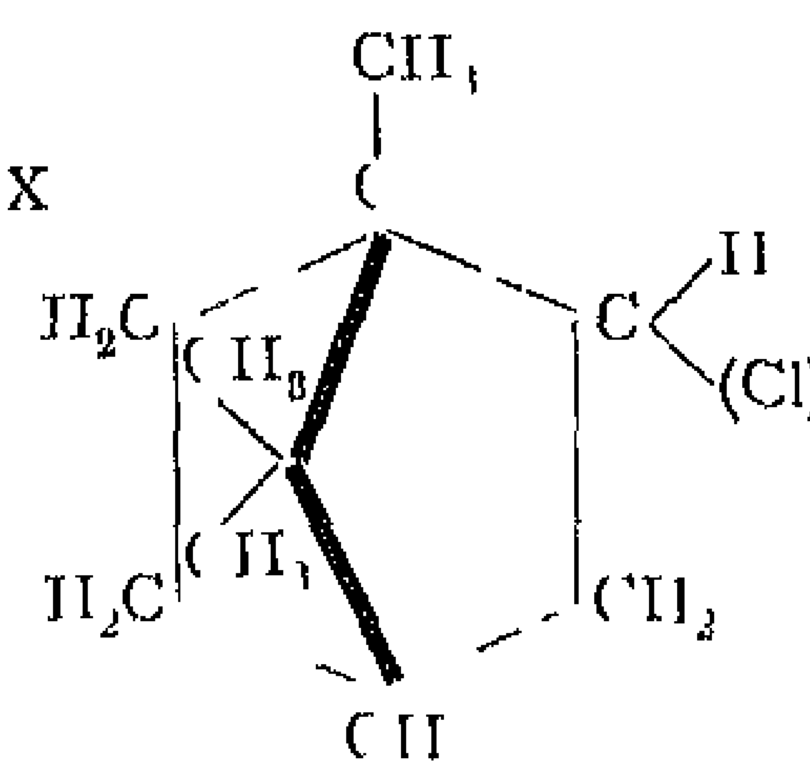
Camphene Camphene hydrochloride Isobornyl chloride

VIII*a*



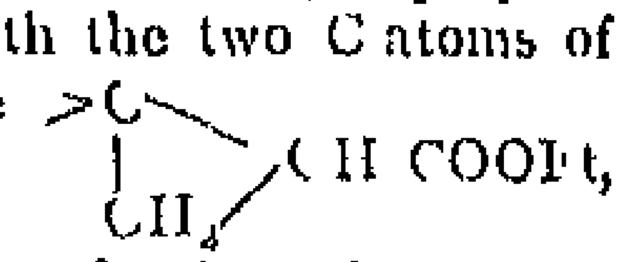
Isobornyl chloride

IX



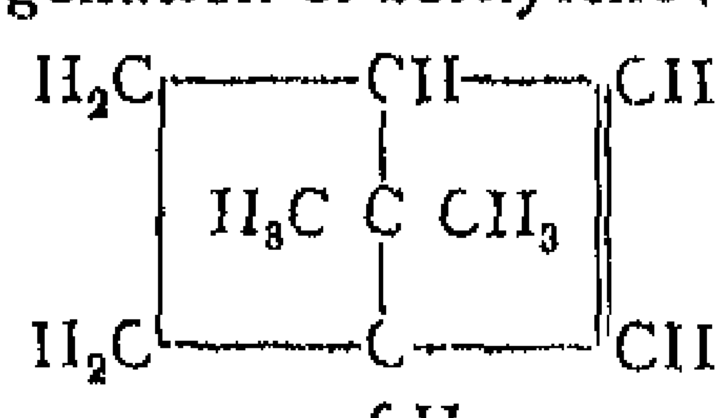
Bornyl chloride

As may be seen from its formula, camphene is not related directly to camphane. An unsaturated derivative of camphane is *bornylene* (see below), which may be prepared by treating bornyl iodide with alkalis The structures assigned to camphene and bornylene are confirmed by their reactions with diazo acetic ester With unsaturated compounds this ester normally yields nitrogen and a cyclopropane derivative, formed by union of the residue >CH COOEt with the two C atoms of the double bond Camphene should thus give a structure

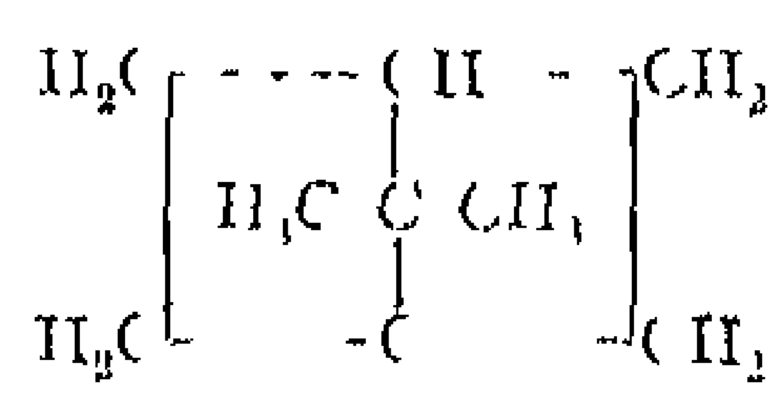


which on oxidation should yield 1 1 2-tricarboxylic acid of cyclopropane Similarly bornylene should yield 1 2 3-tricarboxylic acid Both of these changes have been found to take place [2]

Camphane, $C_{10}H_{18}$, is dihydro-bornylene, since it is formed by the hydrogenation of bornylene.



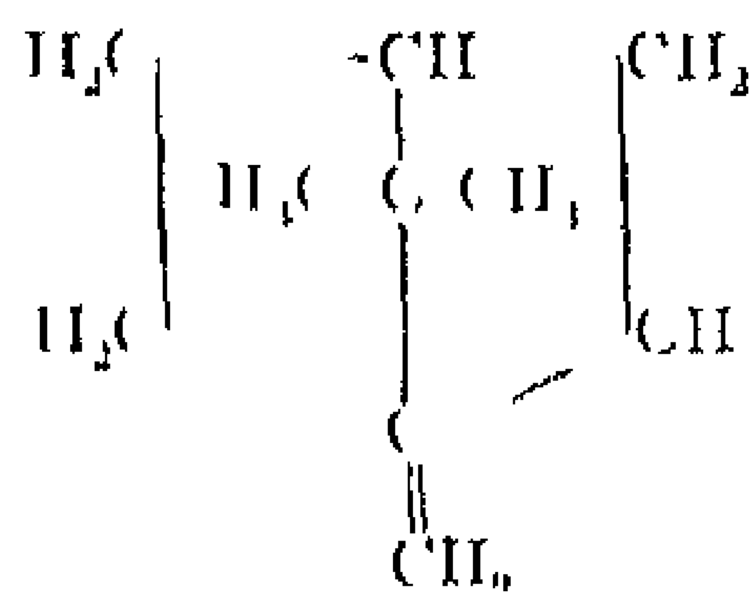
Bornylene



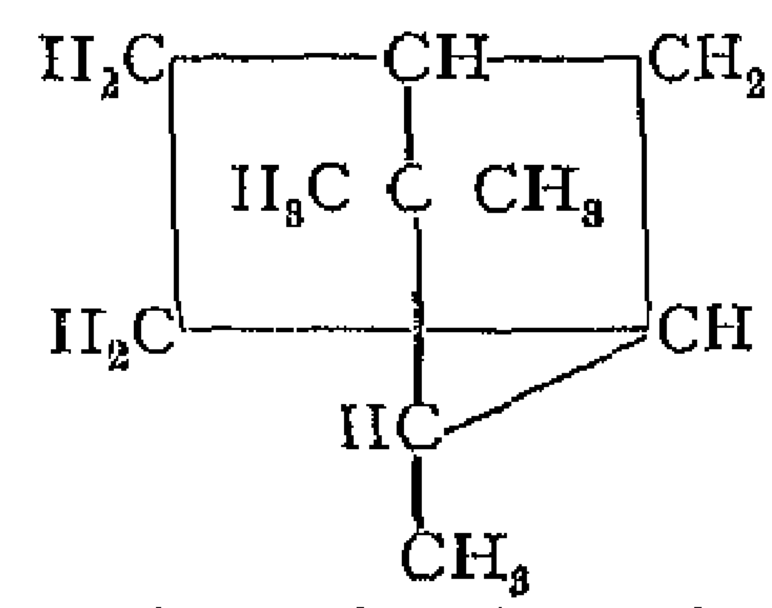
Camphane (dihydro bornylene)

[1] A Hesse, *Ber*, 1906, 39, 1136 For the conversion of borneol or isoborneol into camphene, see Lipp, *Ber*, 1920, 53, 769 [2] Büchner und Weigand, *Ber*, 1913, 46, 258, 2013

whereas camphene corresponds to isocamphane[1]



Camphene



Dihydro camphene (isocamphane)

Camphane is obtained from the bornyl chloride and isobornyl chloride already described. Both of these are readily converted into the magnesium compounds, which on decomposition with water yield camphane.[2] The latter melts at 153°, boils at 160°, and very readily sublimes. Camphane is also produced from borneol when the hydroxyl group is replaced by iodine, and the resulting bornyl iodide is reduced. It is optically inactive and thus possesses a symmetrical structure.

Alcohols and Ketones

Borneol, Borneo camphor, *camphol*, $C_{10}H_{17}\cdot OH$ (formula V, p. 475), melts at 203° and boils at 212°. It exists in nature in the *d*-, *l*-, and *r*-forms. d-*Borneol* is found in a tree, *Dryobalanops camphora*, growing in Sumatra and Borneo, and also in rosemary and spike oils; *l*-borneol and the inactive variety occur in valerian oil. The formation of borneol from pinene and camphene hydrochlorides has already been described. It is related to ordinary camphor as a secondary alcohol to the corresponding ketone, and hence may be converted into camphor by oxidation with nitric acid or prepared from it by reduction with sodium and alcohol. Borneol resembles camphor in smell and burning taste. When warmed with potassium bisulphate it parts with water and yields camphene. It has already been mentioned that bornyl chloride is identical with "pinene hydrochloride". *Isoborneol*, m. p. 212°, is a stereoisomeride of borneol; it may be obtained in the form of its acetate by warming camphene with glacial acetic acid and concentrated sulphuric acid at 50 to 60°. If isoborneol dissolved in xylene is treated with sodium, it is transformed into *borneol*. With oxidising agents such as permanganate, ozone, chlorine or oxides of nitrogen, it is readily converted into camphor.

Camphor, Japanese camphor, $C_{10}H_{16}O$, has until recently been obtained exclusively from the camphor tree, *Laurus camphora*, growing in Japan (particularly in Formosa) and China. For this purpose the wood is heated with water, when camphor and camphor oil pass over with the steam. The vapours are condensed in a

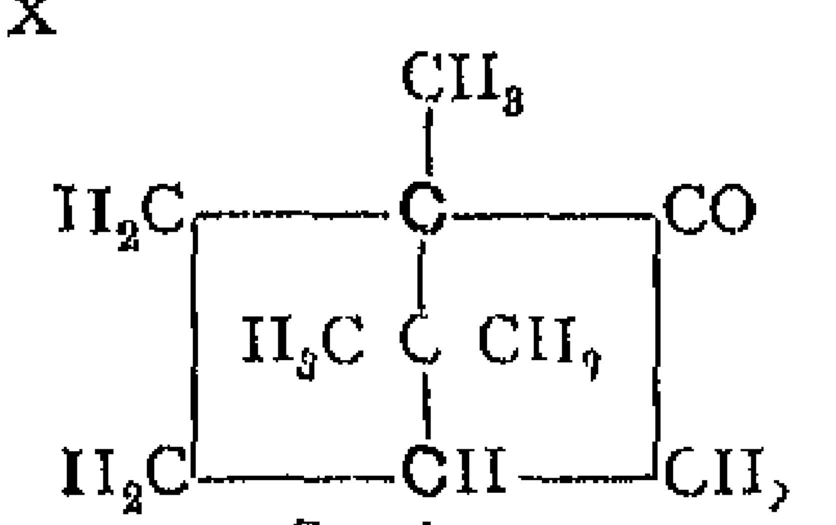
[1] The nomenclature of this group, which is the result of its historical development, is confusing and requires modification. [2] A. Hesse, *Ber.*, 1906, **39**, 1128.

suitable manner and the camphor is removed and purified by sublimation. It forms a colourless, transparent mass of characteristic smell and burning taste, m.p. 175° and b.p. 209°. In alcoholic solution it is dextrorotatory. The world's consumption of camphor is considerable, since it is used in the manufacture of celluloid, explosives and perfumes, and also in medicine. For this reason the industrial preparation of camphor from pinene (p. 480) is of great importance. With the exception of that used for therapeutic purposes, the demand for camphor in Germany is almost entirely met by the artificially prepared product.

l-*Camphor*, the optical antipode of *d*-camphor, occurs in the oil of *Matricaria parthenium*, and apart from the sign of its rotation, shows the same properties as ordinary camphor. By mixing the two antipodes, *r*-camphor, m.p. 178°, is obtained, identical with that produced by the oxidation of *r*-borneol or *r*-camphene.

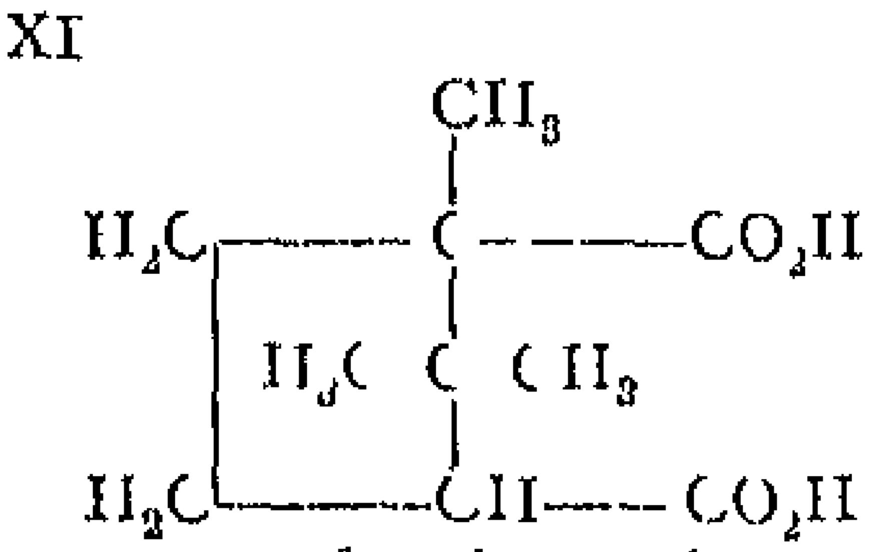
Constitution of Camphor.—The first suggestion as to the constitution of camphor was advanced in 1859 by Berthelot, and for the next forty years numerous workers were engaged on the problem. Information has been gained chiefly by the degradation of the camphor molecule by oxidation, and a series of detailed investigations on these lines finally led Bredt[1] to put forward a constitution (formula X) which is now generally accepted as correct.

X



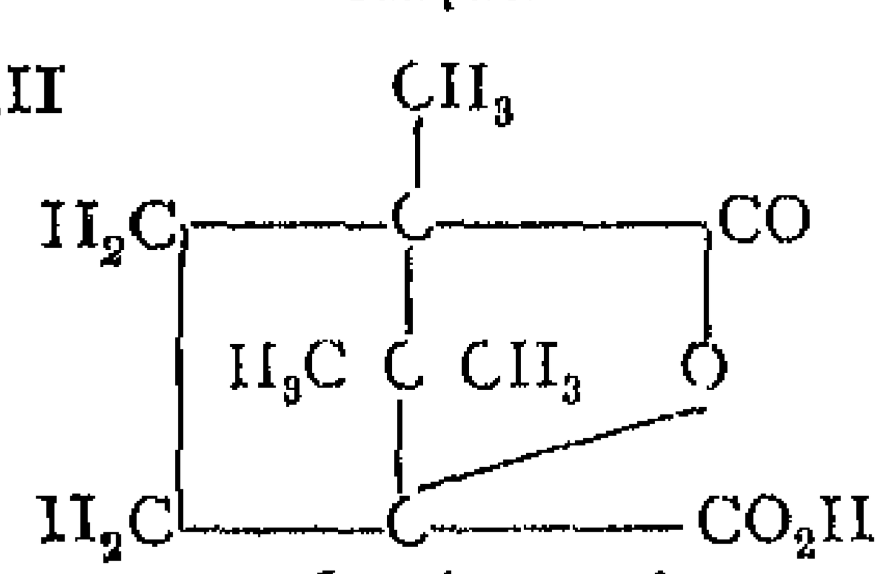
Camphor

XI



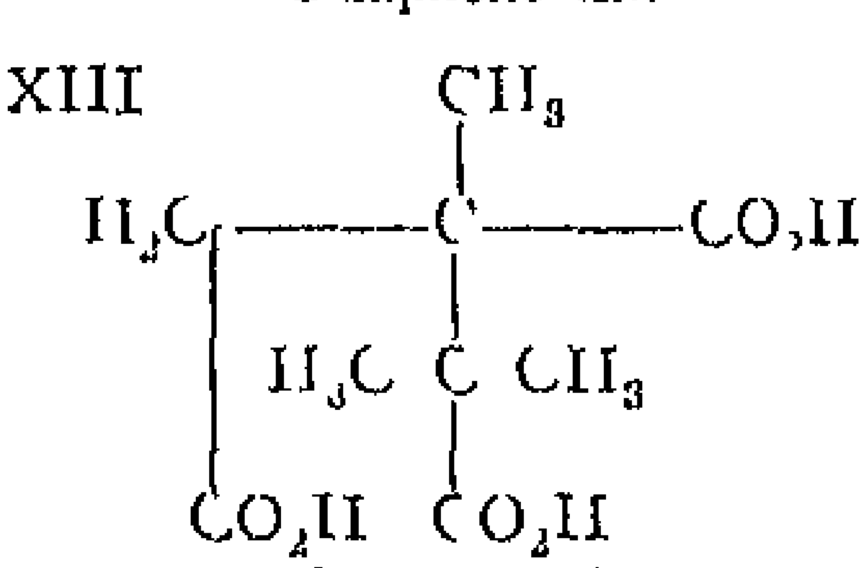
Camphoric acid

XII



Camphanic acid

XIII



Camphoronic acid

The oxidation of camphor with nitric acid leads to the formation of *camphoric acid*, $C_{10}H_{16}O_4$, *camphanic acid*, $C_{10}H_{14}O_4$, and *camphoronic acid*, $C_9H_{14}O_6$, as chief products. These three acids represent different stages of oxidation, and camphoronic acid itself may be obtained by the continued oxidation of either of the other two.

[1] Bredt, *Ber.*, 1893, 26, 3047; 27, 2092; 28, 316; *Ann.*, 1896, 292, 55; 299, 131. See also Lapworth, *B. A. Rep.*, 1900, 299.

Two facts established by Bredt are of special significance in connection with the constitution of camphoronic acid. It is a tribasic acid which resembles tricarballylic acid in its properties. On slow oxidation it breaks up mainly to form carbon dioxide, isobutyric acid and trimethyl-succinic acid. From this behaviour Bredt concluded that camphoronic acid was trimethyl tricarballylic acid, a view confirmed later by its synthesis by Perkin and Thorpe.[1]

$$2\left[\begin{array}{l}(CH_3)_2C\text{—}COOH\\ \quad\quad\;\;\vert\\ CH_3\text{—}C\text{—}COOH\\ \quad\quad\;\;\vert\\ \quad\;\; H_2C\text{—}COOH\end{array}\right]$$

Camphoronic acid

$$= \begin{array}{l}(CH_3)_2C\cdot CO\\ \quad\quad\;\vert\\ CH_3\cdot HC\cdot CO\end{array}\!\!>O + 2(CH_3)_2CH\cdot CO_2H + H_2O + 2CO_2 + C$$

Trimethyl succinic anhydride — Isobutyric acid

Since camphoronic acid is an oxidation product of camphanic acid, camphoric acid and camphor, it may be concluded that the carbon frame-work of camphoronic acid is present in each of these compounds, thus leading to the formulæ shown above. Trimethyl-succinic acid has also been prepared directly from camphoric acid by oxidation with chromic acid. The constitution of camphoric acid has in addition been confirmed synthetically (see below).

The ketonic character of camphor is proved by the formation of an oxime, $C_9H_{16}:C:NOH$ (m.p. 118°, b.p. 249°), and the position of the CO-group is shown by the conversion of camphor into carvacrol, $C_{10}H_{14}O$ (see p. 413), on boiling with iodine. In the latter compound the hydroxyl is in the ortho-position to a methyl group. The presence of the group $CH_2\cdot CO$ in camphor follows from the production of *isonitroso-camphor* (m.p. 153°) on treatment with amyl nitrite and sodium alcoholate. When this substance is boiled with dilute sulphuric acid it yields *camphor-quinone* (m.p. 198°).

$$C_8H_{14}\!\!<\!\begin{array}{l}CH_2\\ \vert\\ CO\end{array} \qquad C_8H_{14}\!\!<\!\begin{array}{l}C:NOH\\ \vert\\ CO\end{array} \qquad C_8H_{14}\!\!<\!\begin{array}{l}CO\\ \vert\\ CO\end{array}$$

Camphor — Isonitroso camphor — Camphor quinone

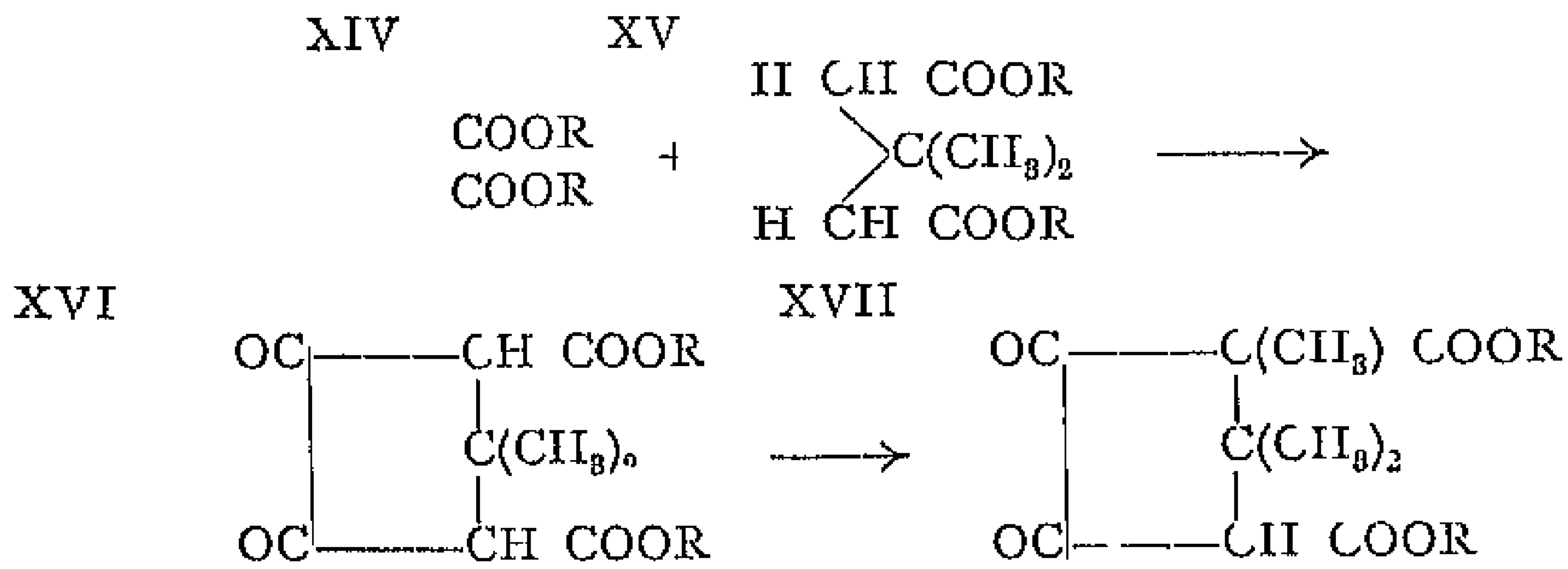
Among other reactions camphor yields *p*-cymene by loss of water when it is heated with P_2O_5.

Synthesis of Camphor.—The most convincing proof of Bredt's formula for camphor is provided by Komppa's synthesis[2] of camphoric acid, from which camphor itself had previously been obtained.[3] The

[1] *J. C. S.*, 1897, 71, 1169. [2] Komppa, *Ann.*, 1909, 368, 126; 370, 209. [3] Bredt and Rosenberg, *Ann.*, 1896, 289, 1.

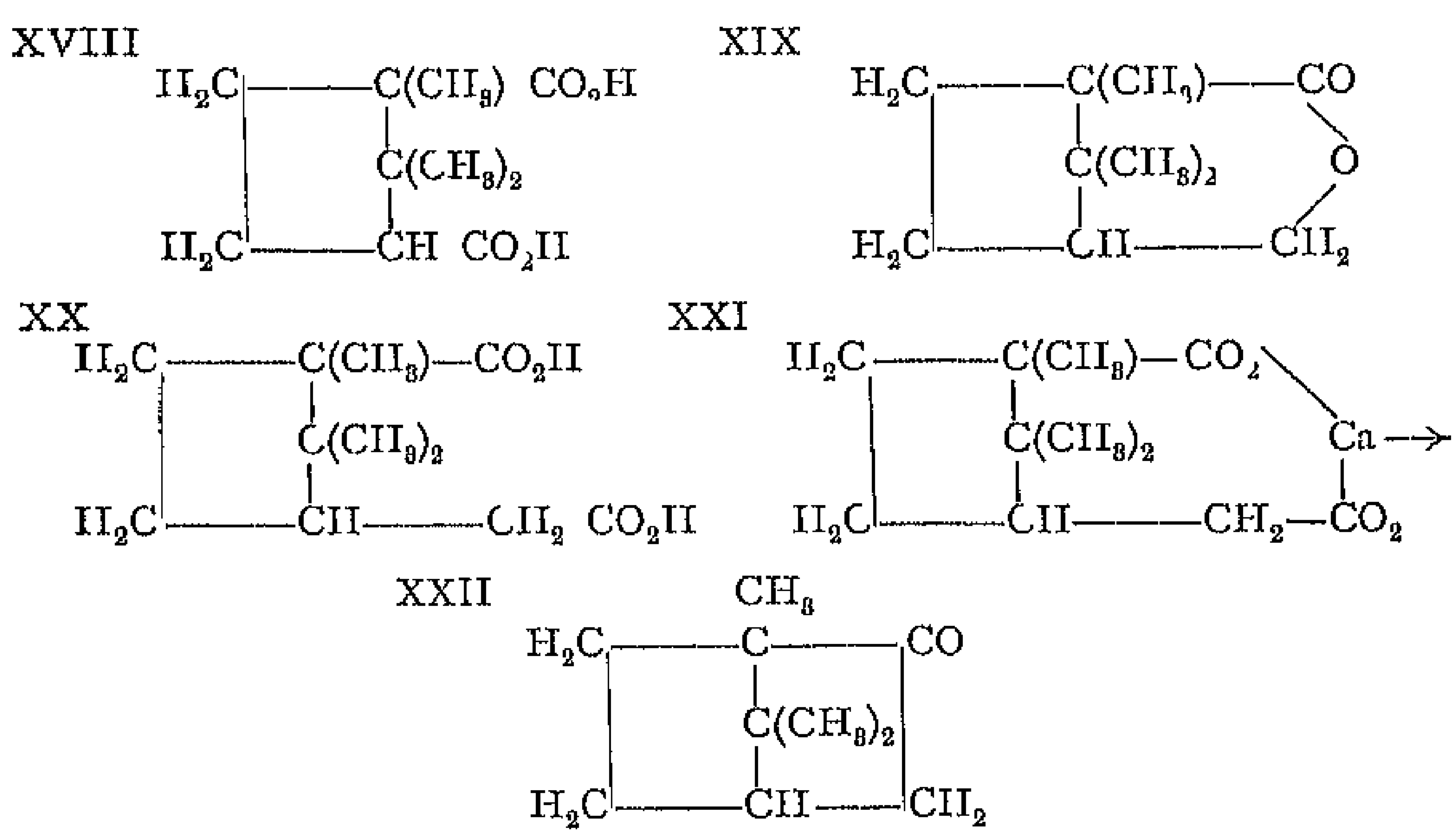
method employed was as follows The dimethyl ester of $\beta\beta$-dimethylglutaric acid (XV) was condensed with oxalic ester (XIV) to give diketo-apocamphoric ester (XVI) From this, by treatment with metallic sodium and methylation with methyl iodide, was obtained diketo camphoric ester (XVII), which by way of various intermediate compounds was reduced to r-*camphoric acid* (XVIII), m p 200° to 202°

XIV XV XVI XVII



Camphoric anhydride, when treated with sodium amalgam, can also be converted into the lactone, campholide (XIX), which with potassium cyanide yields the nitrile of homocamphoric acid (XX) The calcium salt of the latter, on distillation, finally gives the corresponding ketone, camphor (XXII)

XVIII XIX XX XXI XXII



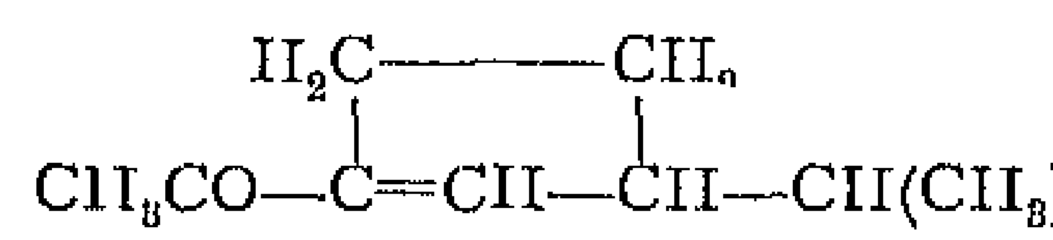
Another synthesis of camphoric acid has been effected by Perkin and Thorpe[1]

Camphor is now prepared industrially from pinene The latter can be converted in a variety of ways into borneol or isoborneol (*e g*, pinene → bornyl chloride → isobornyl acetate → isoborneol)

[1] *J C S*, 1906, 89, 795

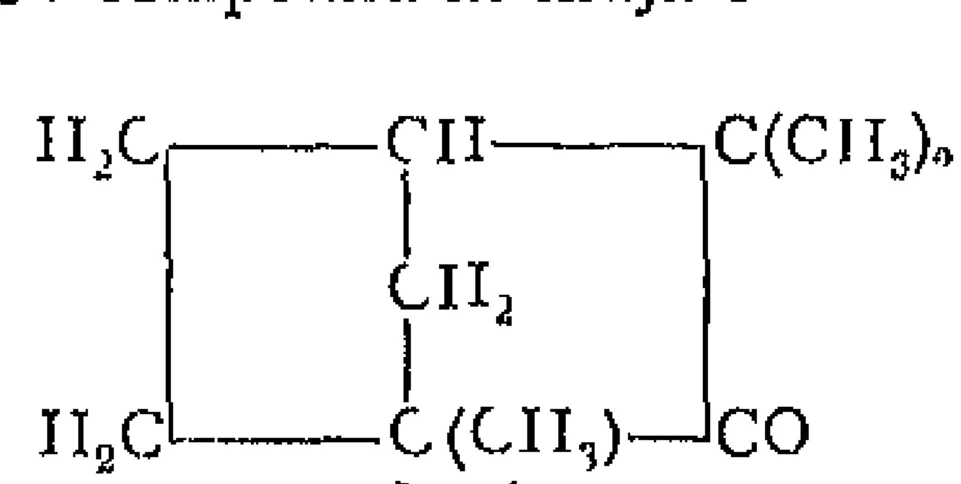
and thence by oxidation into camphor. The name "artificial camphor" as applied to bornyl chloride is unfortunate.

Contrary to the earlier view, the compound known as *isocamphor* is now found to possess an entirely different structure to that of camphor.[1] It contains a five-membered ring and is a Δ^1-1-acetyl-isopropyl-cyclopentene of the formula

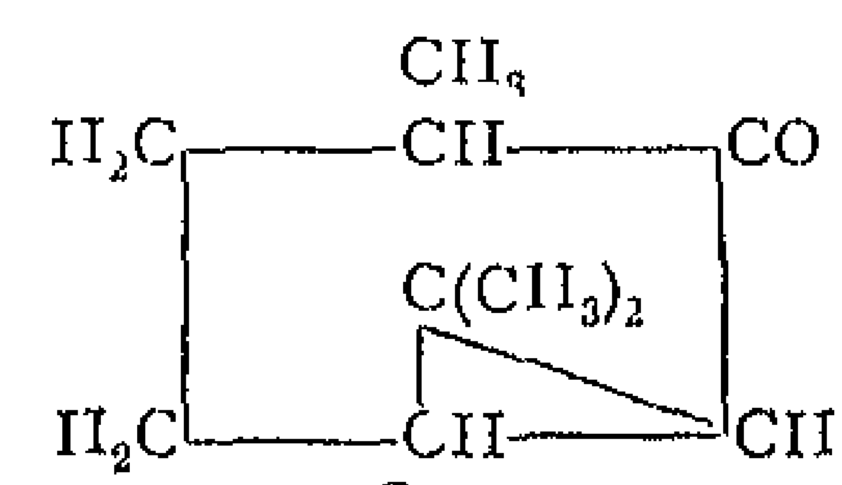


Other ketonic derivatives of the dicyclic terpenes are fenchone and carone.

Fenchone,[2] m.p. 5°, b.p. 192° to 194°, is very similar to camphor in its behaviour. It is found as the *d* enantiomorph in fennel oil, and as the *l*-compound in thuja oil.



Fenchone



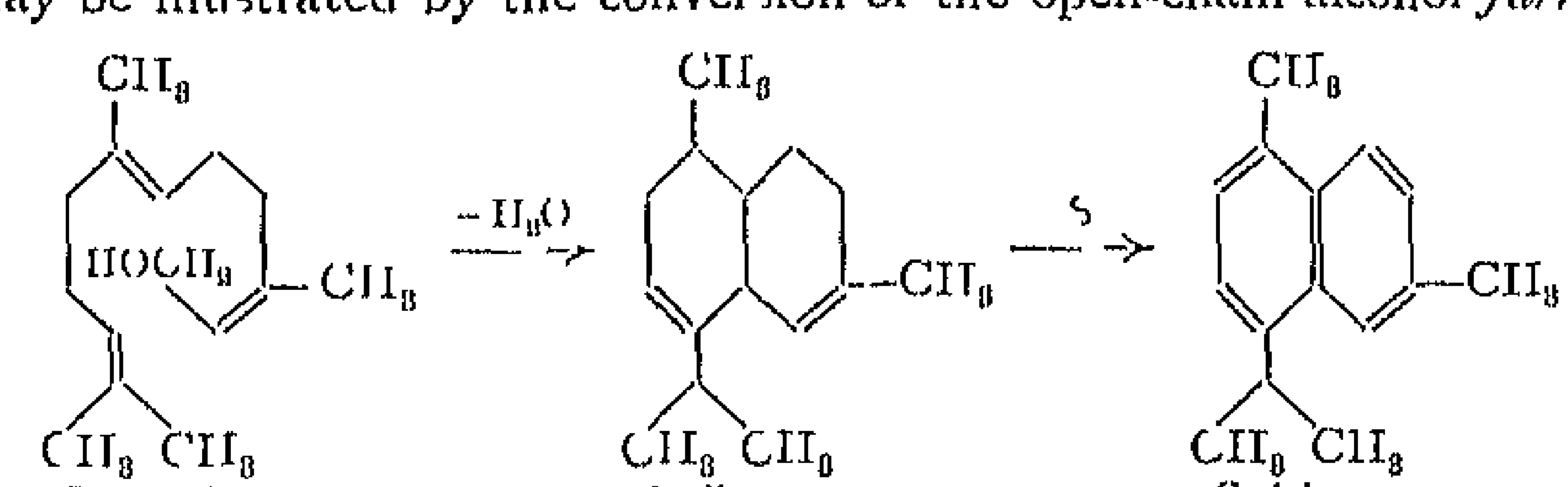
Carone

Carone (b.p. 100°/15 mm.) is a ketone derived from the unknown hydrocarbon, carane. It does not occur naturally but can be prepared from carvone.

Sesquiterpenes and Diterpenes

Considerable progress has been made during the last few years in the investigation of higher terpenes, especially the sesquiterpenes.

Sesquiterpenes include hydrocarbons of the formula $C_{15}H_{24}$ and their oxygen derivatives, and are found widely distributed in essential oils. Some of the members of this group are **open-chain compounds** (*farnesol*), others are **monocyclic** (*bisabolene*, *zingiberene*) and still others **dicyclic** (*cadinene*, *eudesmol*). Much of our knowledge of these compounds is due to Ruzicka.[3] The relationships among the sesquiterpenes may be illustrated by the conversion of the open-chain alcohol *farnesol*

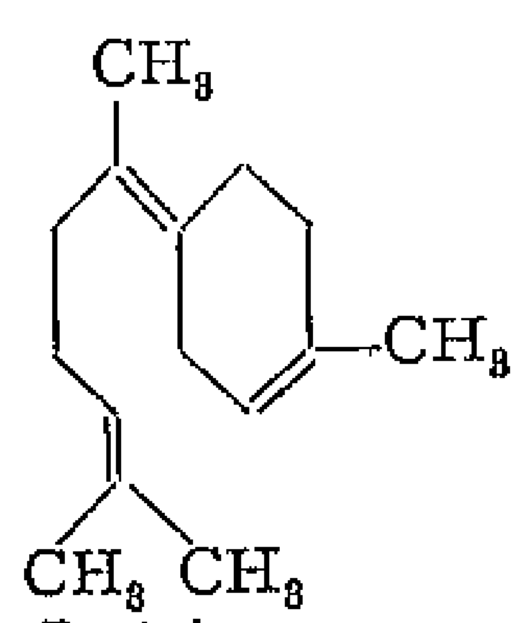


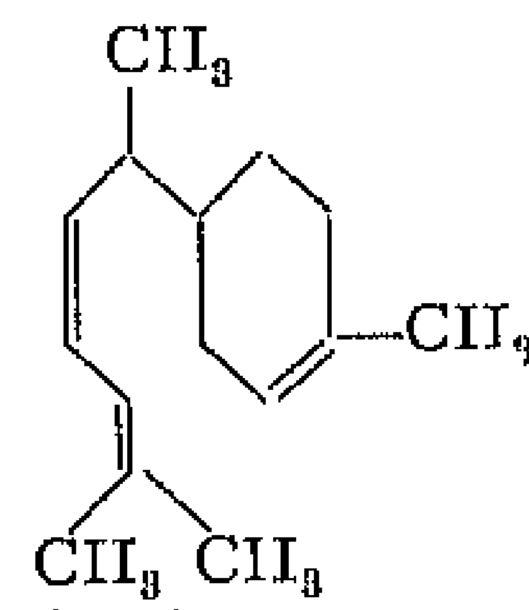
Farnesol Cadinene Cadalene

[1] Wallach and Schlubach, *Ann.*, 1912, 392, 69. [2] Wallach, *Ann.*, 1909, 369, 63. [3] See L. Ruzicka, *Über Konstitution und Zusammenhänge in der Sesquiterpenreihe* (Berlin, 1928).

by loss of water into the dicyclic hydrocarbon *cadinene* By fusion with sulphur (Vesterberg's dehydrogenation method) the latter has been converted into cadalene, 1 6-dimethyl-4-isopropyl-naphthalene, thus giving valuable information as to its structure

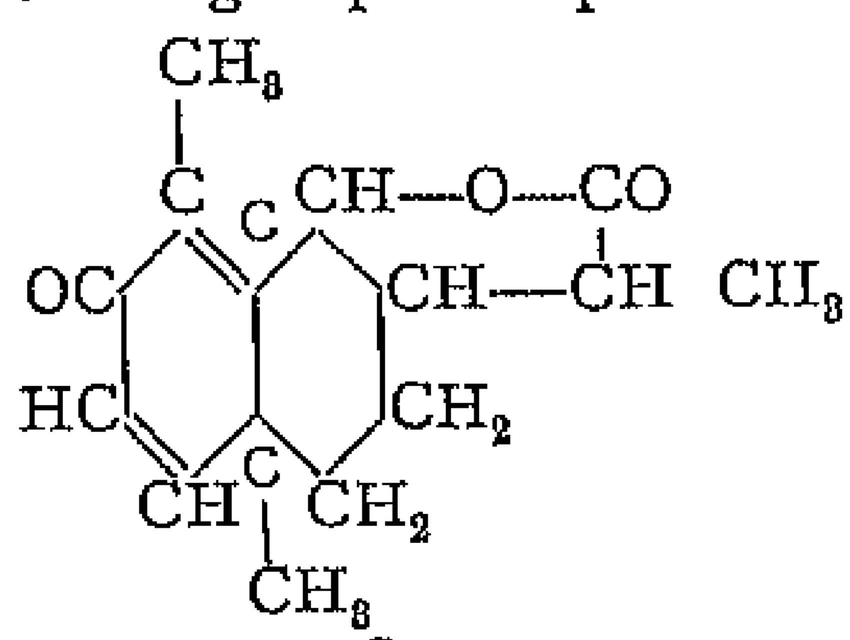
Among *monocyclic sesquiterpenes* may be mentioned *bisabolene* (from oil of lemons) and its isomeride *zingiberene* (in oil of ginger) The former may be obtained from farnesol by gentle warming with strong acids

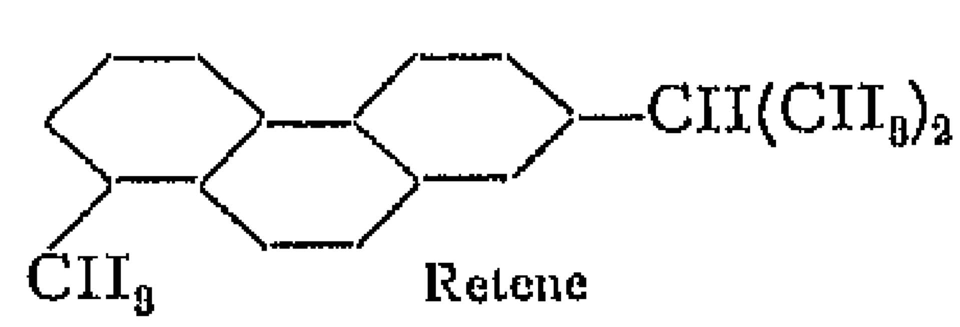

Bisabolene


Zingiberene

The *dicyclic sesquiterpenes* are related to naphthalene in much the same manner as the terpenes are to benzene, some (e g *cadinene*, in oil of cubebs) being derived from cadalene, others (e g *eudesmol*, in eucalyptus oil) from eudalene, 1-methyl-7-isopropyl naphthalene, and similar types

Santonin, $C_{15}H_{18}O_3$, m p 170°, $[\alpha]_D = -171°$, is the active constituent of wormseed (*Artemisia Santonica*) Clemo and Haworth[1] have shown that it possesses the annexed formula, a modification of an earlier suggestion of Cannizzaro It is thus a lactone closely related to the eudesmol group of terpenes


Santonin

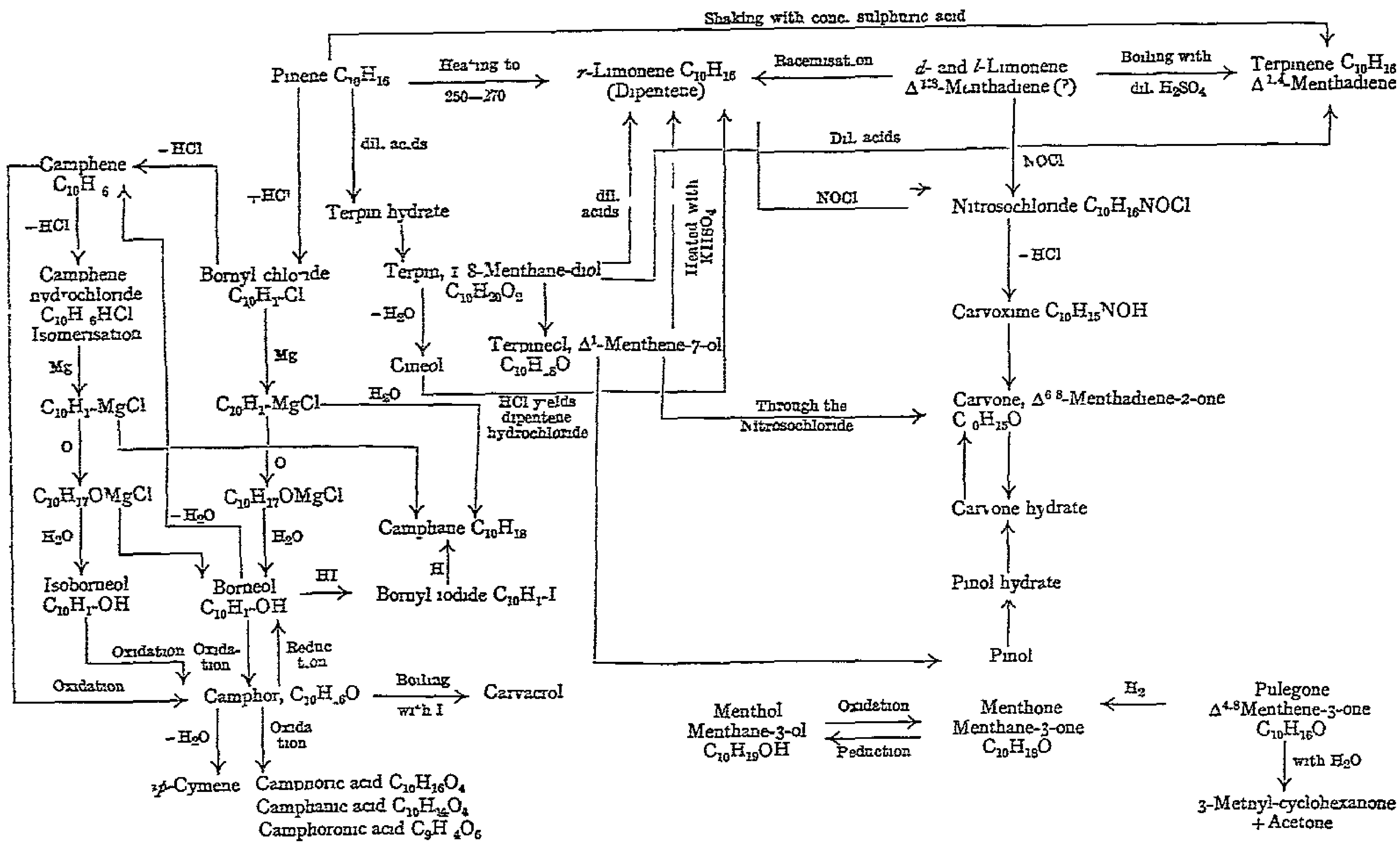

Retene

Comparatively little is known about the **diterpenes**, $C_{20}H_{32}$, which occur chiefly in vegetable resins and balsams The best known representative is the carboxylic compound, *abietic acid*, ($C_{20}H_{30}O_2$), which forms the chief constituent of ordinary rosin (colophonium) On being heated with sulphur abietic acid yields retene, 1-methyl-7-isopropyl-phenanthrene

Squalene,[2] $C_{30}H_{50}$, is an open-chain **dihydro triterpene** obtained from the livers of certain fish

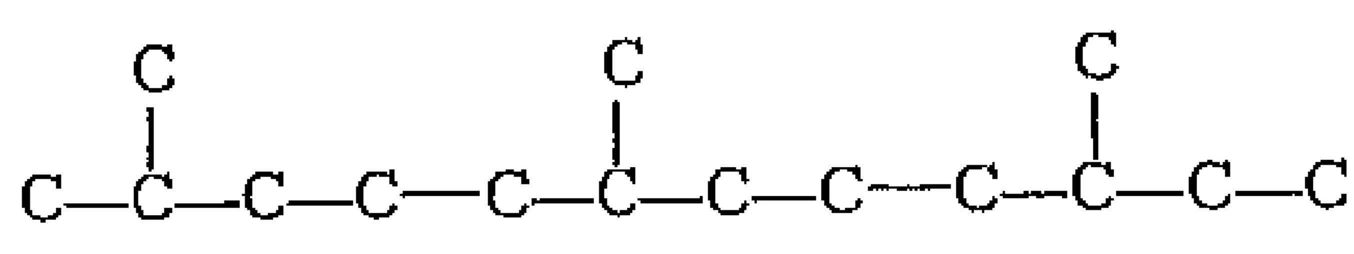
[1] G R Clemo, R D Haworth and E Walton, *J C S*, 1929, 989; 1930, 1110 Clemo and Haworth, *J C S*, 1930, 2579 The above constitution is also adopted by Ruzicka, *Helv Chim Acta*, 1930, 13, 1117 [2] Heilbron and co-workers, *J C S*, 1926, 1630, 3131; 1929, 873, 883

Transformations and Degradations in the Terpene and Camphor Series

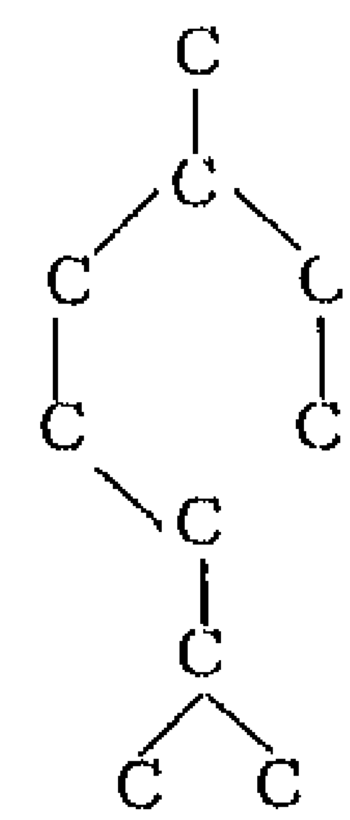


Isoprene and Terpene Structure

Up to the present, all terpenes of known constitution, whether simple or complex, open-chain or cyclic, have been found to possess a molecular structure built up of a complete number of isoprene units



Open chain sesquiterpene



Monocyclic terpene

This relationship possibly indicates a common origin in the form of some reactive 5-carbon compound such as isovaleraldehyde, $(CH_3)_2CH\ CH_2\ CHO$, or of simpler products which may give rise to it, a speculation which is supported by the occurrence of isovaleraldehyde (and of acetone and acetaldehyde) in a number of essential oils It has been suggested that these substances by condensation and reduction may give rise to citral or geraniol and thus to various more complex derivatives[1]

STEROLS AND BILE ACIDS

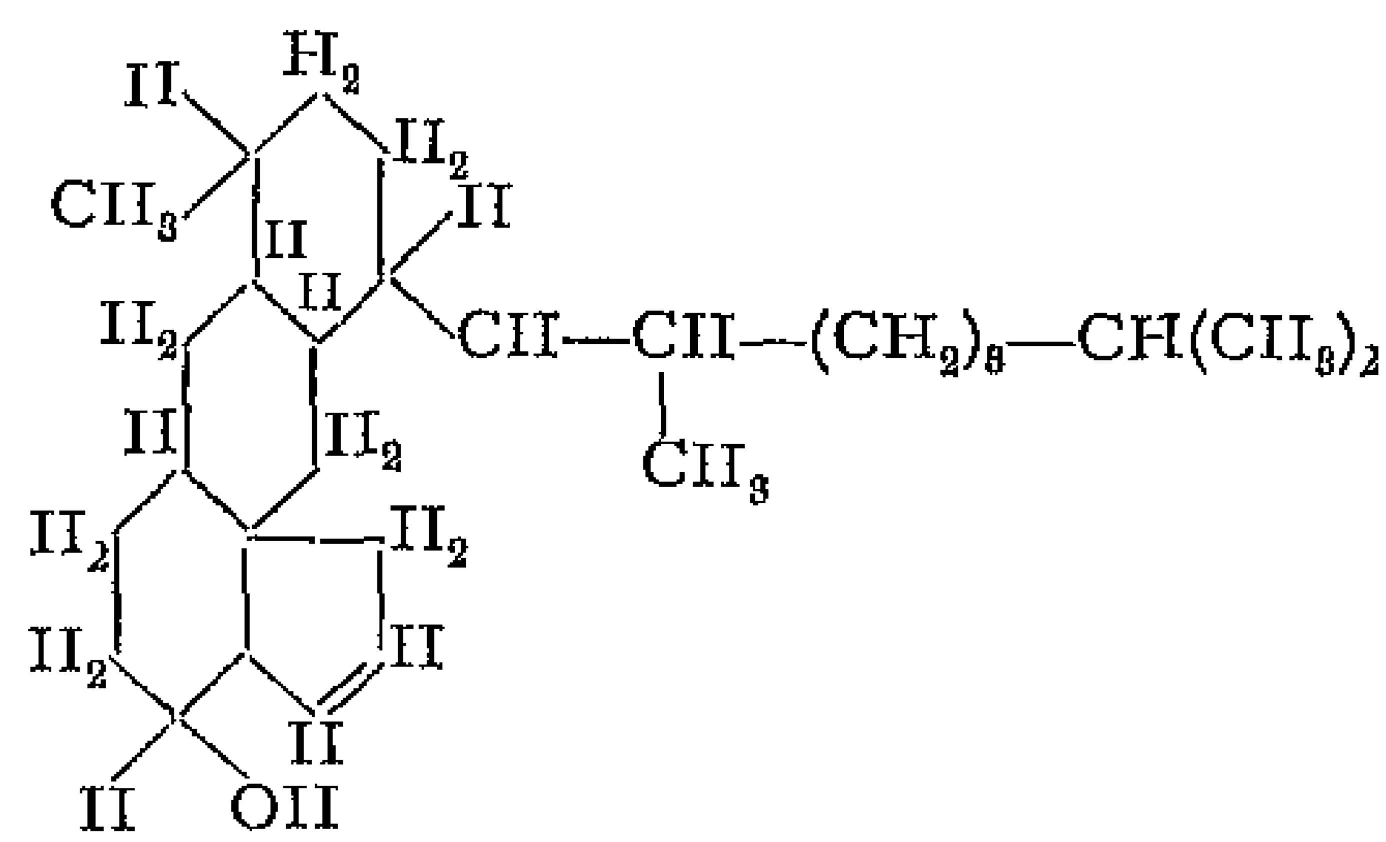
Cholesterol, $C_{27}H_{45}OH$, an unsaturated alcohol, is widely distributed in the human organism, and was first discovered in gallstones In addition to the "typical cholesterol," a number of isomerides have been found (in cow's milk, eggs and the brain of horses) which closely resemble it in properties From the physiological standpoint it is interesting to note that the typical cholesterol never occurs in plants, in which its place is taken by *phytosterol* The sterols are therefore extensively distributed in living nature, and may be regarded as fundamental cell-constituents which are present in every cell capable of evolution Cholesterol is insoluble in water and only dissolves with difficulty in petroleum ether, alcohol, and acetone It is readily soluble in carbon bisulphide, benzene and ether From the latter it crystallises in needles, m p 148 5°

Ergosterol, $C_{27}H_{41}OH$, is a still more unsaturated alcohol which may be obtained from either ergot (p 669) or yeast When irradiated with ultra-violet light or sunlight it yields a product possessing a powerful anti-rachitic (anti-rickets) action, this is probably identical with *vitamin D*[2]

[1] Compare Kremers, *J Biol Chem*, 1922, 50, 31 J Read, "Some Biogenetic Relationships in the Menthone Series," *J S C I*, 1929, 48 (*Chem and Ind*), p 786 [2] Rosenheim and Windaus, *Biochem J*, 1927, 21, 127, 389

During recent years the structure of cholesterol has been investigated in detail, more particularly by Windaus.[1] It may be represented provisionally by formula I.

I



In determining the structure of complex natural products successful use has lately been made of *dehydrogenation processes*. For example, *sulphur* at high temperatures removes hydrogen from hydro-aromatic systems, leading in many cases to the formation of well-defined aromatic compounds (see also p. 482, for the conversion of abietic acid into retene). Disadvantages of the sulphur method are that sulphur may enter into the molecule of the compound under treatment or bring about far-reaching carbonisation. These disadvantages are so strongly marked in the case of cholesterol that no results of value can be obtained. On the other hand, cholesterol and its derivatives may be dehydrogenated comparatively smoothly by means of *selenium*,[2] which reacts in a similar manner to sulphur but less energetically. The use of selenium for this purpose appears to be of general application.

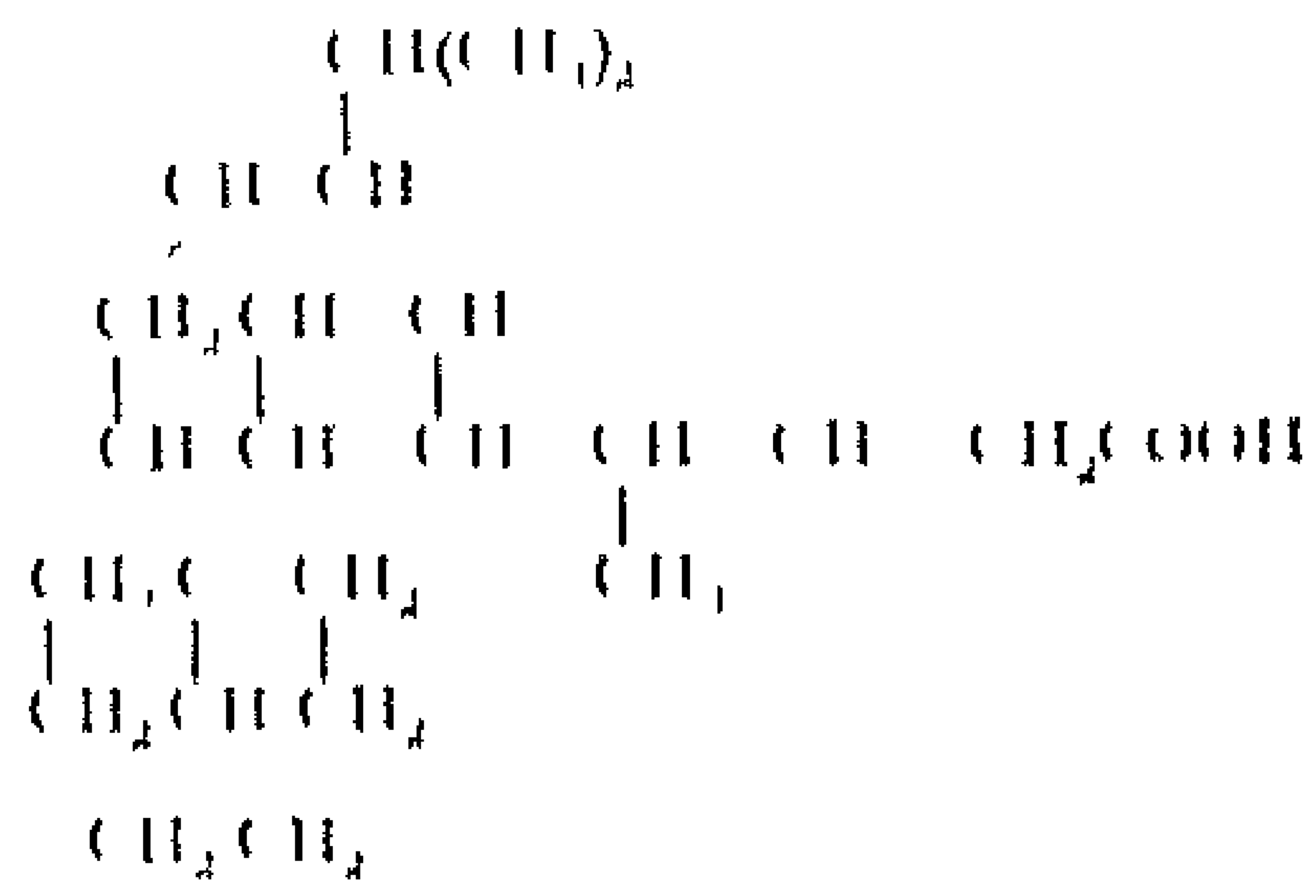
A point of great biological interest is the close relationship of the sterols to other classes of natural products, such as the *bile acids* and *vitamins*, and probably also to the vegetable poisons of the *saponin group* and the poisonous secretion from the skin of the toad.

The **bile acids** present in the bile pass into the intestine and there promote the enzymic disruption of fats. They occur to some extent in peptide union with glycine and taurine (see p. 241). *Cholic acid*, $C_{23}H_{36}(OH)_3COOH$, was isolated by Strecker (1848) from ox-gall in the form of *glycocholic acid* and *taurocholic acid*. Hammarsten isolated *deoxycholic acid*, $C_{23}H_{37}(OH)_2COOH$, from bile in its natural state paired with taurine and glycine. He also showed that cholic acid occurred in the bile of numerous vertebrates. A third monocarboxylic acid, *lithocholic acid*, $C_{23}H_{38}(OH)COOH$, containing less oxygen was discovered in 1911 by Hans Fischer in the gallstones of cattle, and

[1] A. Windaus, *Ber.*, 1927, 60, 133; *Zeit. für physiol. Chem.*, 1923, 180, 113. H. Wieland and co-workers, *Zeit. für physiol. Chem.*, 1926, 161, 80; O. Diels and Gädke, *Ber.*, 1927, 60, 140; *Ann.*, 1927, 459, 1. [2] O. Diels and A. Karstens, *Ber.*, 1927, 60, 2323.

subsequently proved to be a normal constituent of bile in cattle and humans. All three acids can be reduced to *cholanic acid*, $C_{23}H_{39}COOH$.

The close relationship existing between the bile acids and the sterols was first definitely proved by Windaus,[1] who showed that the hydrocarbon coprostane (obtained from coprosterol by way of the chloride) gave cholanic acid when oxidised with chromic acid. Extensive researches carried out by H. Wieland[2] have gone far to elucidate the structural details of the bile acids. According to the latest results, cholanic acid is provisionally formulated as in II.

II. 

XIII

Compounds containing Benzene Nuclei united by Carbon Linkings

Many of the methods described in the foregoing sections for introducing alkyl groups into the benzene nucleus may also be employed for the introduction of phenyl, benzyl and other aromatic groups. In this way compounds are formed containing benzene nuclei linked together directly, or through the medium of one or more carbon atoms. The simplest examples of this kind are in the diphenyl group.

I. DIPHENYL GROUP

Diphenyl, *phenyl benzene*, $C_6H_5 \cdot C_6H_5$, the parent hydrocarbon of this series, is formed when benzene vapour is passed through a red-hot tube. It is best prepared by *Ullmann*'s method, in which iodobenzene is heated to 220° with finely-divided copper:

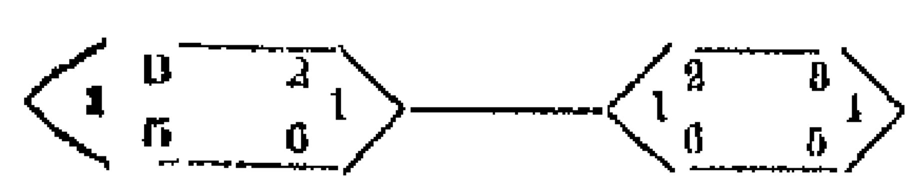
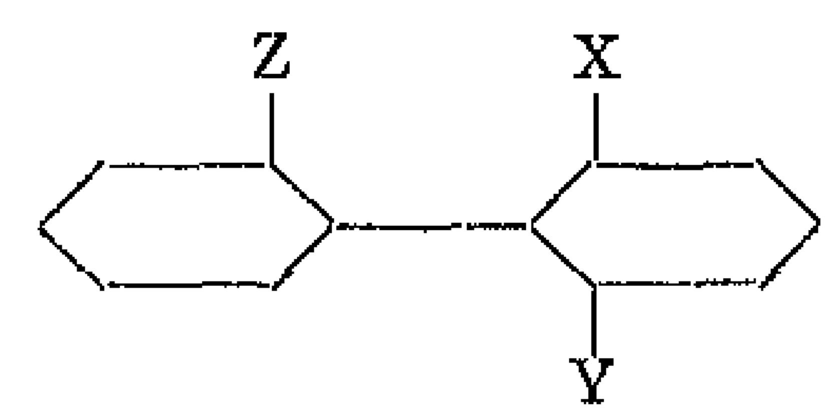
$$2C_6H_5I + 2Cu = C_6H_5 \cdot C_6H_5 + Cu_2I_2$$

[1] Windaus and Neukirchen, *Ber.*, 1919, 52 B, 1915. [2] Compare H. Wieland, *Die Chemie der Gallensäuren*, Nobel Lecture, delivered in Stockholm, December 1928. See also *Zeitschr. f. angew. Chem.*, 1929, 42, 421.

This process recalls Fittig's synthesis, but is of far greater general utility It can be applied successfully to a variety of substitution products of iodobenzene, with the production of symmetrical diphenyl derivatives[1] In the majority of cases the reaction between copper and the iodo-compound proceeds at 210° to 220°, and the constitution of the synthetic product can be deduced directly from that of its components

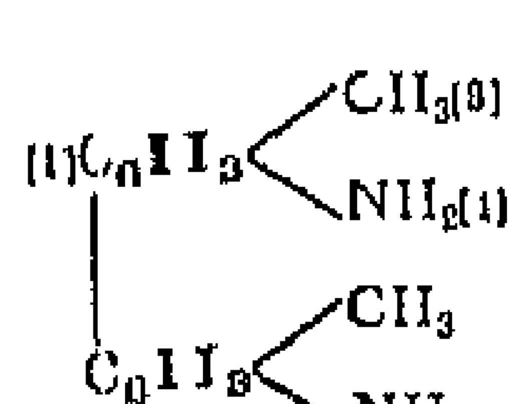
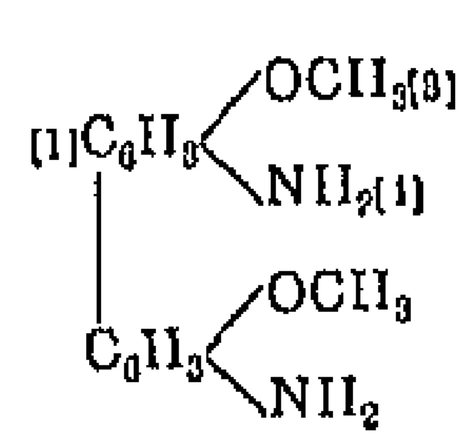
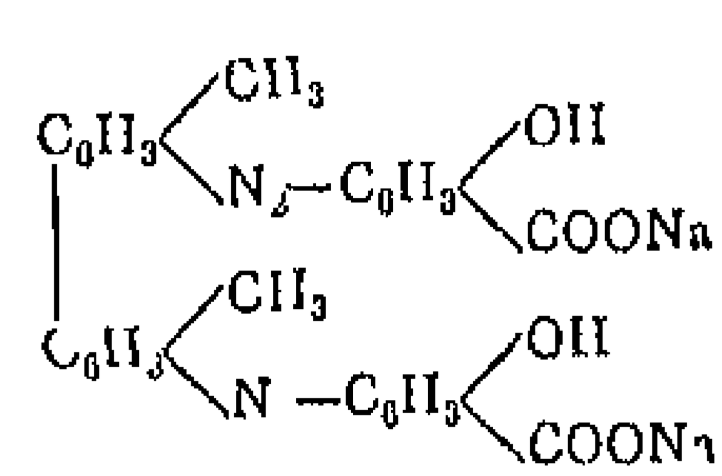
Diphenyl is also found in coal tar It forms colourless crystals which melt at 70°, boil at 254°, and are readily soluble in alcohol and ether With ozone it yields a *tetra-ozonide*

The position of substituents in the diphenyl molecule is usually indicated by numbers as in formula I With two or more substituents it will be seen that there are numerous possibilities of isomerism In addition, isomerism of a new type may occur when three or four of the ortho-positions to the common bond joining the benzene nuclei are substituted as in II (X and Z may also be identical) This isomerism is discussed fully on p 44

I  II 

Benzidine, 4 4′ *diamino-diphenyl*, $NH_2\ C_6H_4\ C_6H_4\ NH_2$, is obtained as described on p 392 by intramolecular rearrangement of hydrazobenzene. In its technical preparation nitrobenzene is reduced with zinc dust and sodium hydroxide, and the hydrazo-benzene so formed is converted into benzidine by heating with acid The compound may either be isolated as the free base by addition of sodium hydroxide, or as the sparingly soluble sulphate Benzidine crystallises from hot water in leaflets, m p 122°, and is largely used in the manufacture of substantive azo-dyes (see p 400 *et seq*) The *sulphonic acids* obtained by the action of concentrated sulphuric acid on benzidine are employed for the same purpose

Tolidine (I), m p 128°, is a homologue of benzidine and is prepared in a similar manner from *o* nitrotoluene, *o* **dianisidine** (II) is obtained from *o* nitroanisole, $C_6H_4(NO_2)OCH_3$

I  II  III 

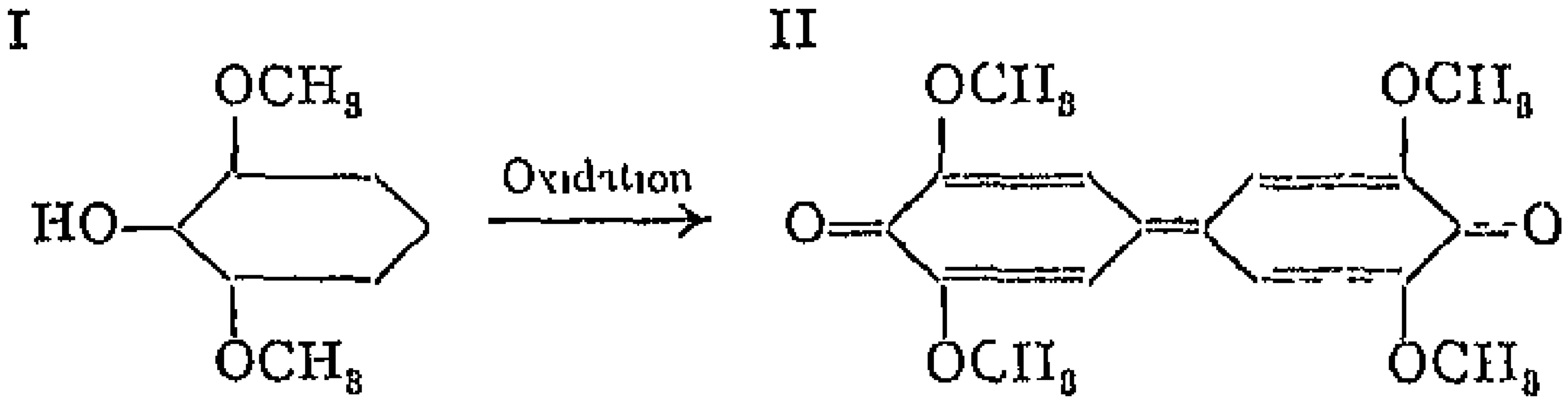
The first of these, on diazotisation and coupling with *a* or *β* napthylamine sulphonic acids, yields the benzo purpurines (B, 4B, 6B) These are red substantive

[1] Compare Ullmann, *Ann*, 1905, 332, 38

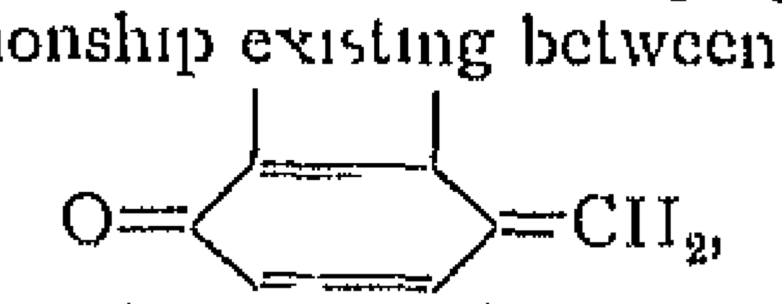
dyes, and are less sensitive to acids than Congo red From diazotised benzidine or tolidine and salicylic acid are obtained yellow substantive dyes known as **chrysamines** (*e g*, compound III) *Diamine black* is prepared by coupling diazotised benzidine or dianisidine with aminonaphthol sulphonic acid G (2 8 6) in alkaline solution

Hexahydroxy-diphenyl, $(HO)_3C_6H_2\ C_6H_2(OH)_3$, crystallises from hot water in colourless needles, which darken above 200° and then gradually melt with decomposition It is formed when pyrogallol dissolved in aqueous baryta is oxidised in air A second hexahydroxy-diphenyl can be obtained from coerulignon **Coerulignon** or *cedriret*, $C_{16}H_{16}O$, is a bluish-violet powder obtained during the purification of crude wood vinegar with potassium bichromate It is regarded as a **tetramethoxy-diphenoquinone** (II), a view confirmed by its synthesis by A W Hofmann, by oxidation of the pyrogallol dimethyl ether occurring in beech tar Since this ether had been proved[1] to possess the structure I, coerulignon must be written as II

I II



On reduction coerulignon yields **hydro-coerulignon,** which is represented as a tetramethyl ether of hexahydroxy-diphenyl It melts at 190°, and on heating with concentrated hydrochloric acid is converted into a hexahydroxy-diphenyl, differing from that obtained by oxidation of pyrogallol

Other *diphenoquinones* or coerulignons have been prepared by Auwers,[2] who has shown the close relationship existing between these compounds and the *methylene-quinones,*  which play an important rôle as the parent substances of many dye-stuffs, and as intermediate products in the transformations of pseudophenols These two classes resemble one another in chemical behaviour, particularly in their strong additive properties

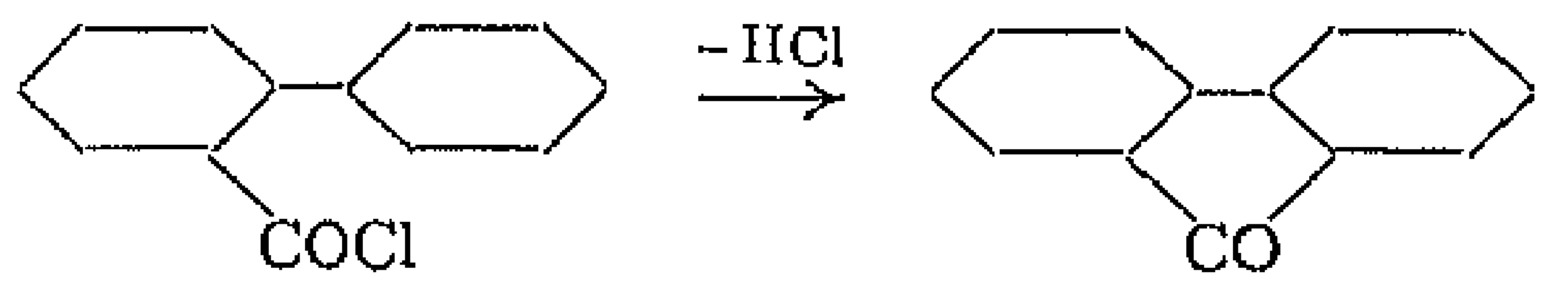
Diphenyl-2-carboxylic acid, m p 111°, is obtained by fusing *fluorenone* (p 493) with potassium hydroxide

$$C_6H_4\overset{CO}{\diagdown\!\diagup}C_6H_4 + KOH = C_6H_5{-}C_6H_4\ COOK$$

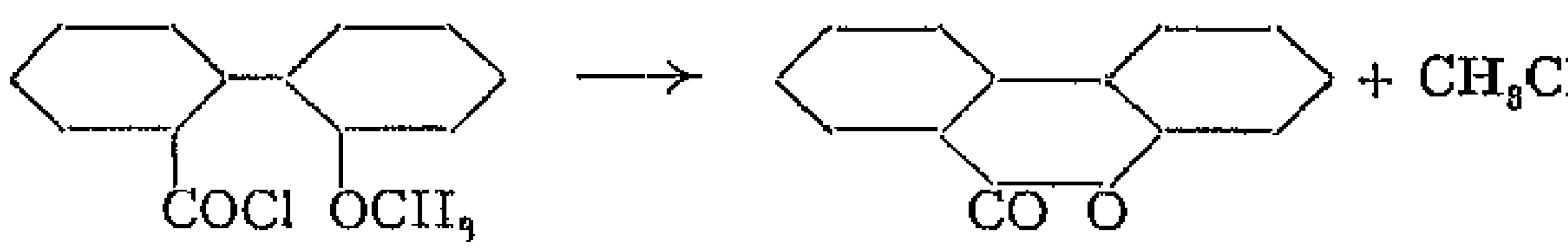
On treatment with strong sulphuric acid it loses water to give

[1] Herzig and Pollak, *Monat f Chem*, 1904, **25**, 501 [2] Auwers and Markovits, *Ber*, 1905, **38**, 226

fluorenone. A similar ring closure is undergone by the acid chloride on distillation.[1]



The acid chloride of *2'-methoxy-diphenyl-2-carboxylic acid* loses methyl chloride spontaneously at ordinary temperatures to form the lactone of the 2'-hydroxy acid.[2]



These reactions are promoted by the proximity of the substituents in the 2 2'-positions (see also isomerism of diphenyl derivatives, p. 44).

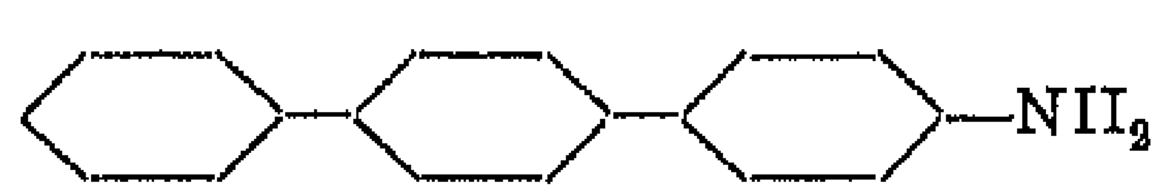
Diphenic acid, *diphenyl-2 2'-dicarboxylic acid,* is obtained by oxidising phenanthraquinone with a mixture of potassium bichromate and sulphuric acid. This reaction has given valuable information as to the constitution of phenanthrene.

Phenanthraquinone Diphenic acid

In the same manner substituted diphenic acids may be prepared from substituted phenanthraquinones.[3]

Another method of preparing diphenic acid is by the action of an ammoniacal solution of cuprous oxide on diazotised anthranilic acid.[4] Diphenic acid melts at 229°. When heated with soda lime it yields diphenyl, and on strong oxidation is converted into phthalic acid.

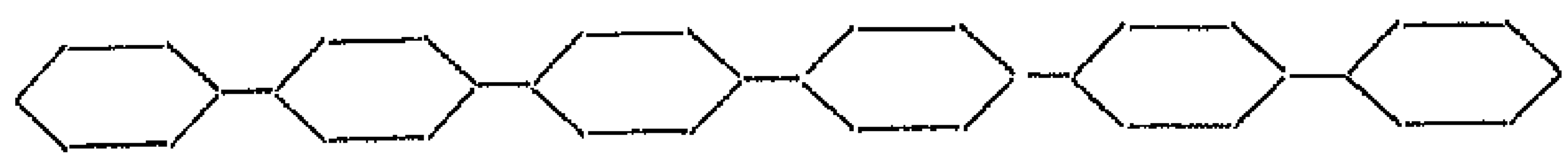
A number of hydrocarbons built up of a series of benzene rings linked together in the *p*-positions have recently been prepared. **Terphenyl,** p-*diphenyl-benzene,* m.p. 210°, was obtained by the interaction of azobenzene, benzene, hydrogen chloride and aluminium chloride. An intermediate product in the process is *amino diphenylbenzene,* which was deaminated in the usual way (p. 394).



By converting the amino- into the corresponding iodo-compound and

[1] C. Graebe and Rateanu, *Ann.*, 1894, **279**, 261. [2] H. G. Rule and E. Bretscher, *J. C. S.*, 1927, 925. [3] J. Schmidt and co-workers, *Ber.*, 1903, **36**, 3729; **37**, 3551. [4] Vorländer and Meyer, *Ann.*, 1902, **320**, 122.

heating the latter with silver powder at 330° (*Ullmann's* method) **sexiphenyl**, m p 475°, was prepared [1] These are colourless hydrocarbons which sublime well below their melting-points



II —DIPHENYL-METHANE AND FLUORENE GROUPS

Diphenyl-methane, *benzyl-benzene*, $C_6H_5 \cdot CH_2 \cdot C_6H_5$, forms needles, m p 26° and b p 262°, and has an odour of oranges It may be obtained by the following methods —

1 By the action of benzyl chloride, or of methylene chloride, on benzene in the presence of aluminium chloride

$$C_6H_5 \cdot CH_2Cl + H \cdot C_6H_5 \xrightarrow{-HCl} C_6H_5 \cdot CH_2 \cdot C_6H_5 \xleftarrow{-2HCl} 2C_6H_5 \cdot H + CH_2Cl_2$$

Various substitution products of benzene may also be employed (*e g* homologues, phenols, tertiary amines), leading to the formation of ring-substituted diphenyl-methanes

2 By the condensation of benzyl alcohol with benzene under the influence of concentrated sulphuric acid

$$C_6H_5 \cdot CH_2OH + HC_6H_5 = C_6H_5 \cdot CH_2 \cdot C_6H_5 + H_2O$$

Homologues of diphenyl-methane containing substituents in the methylene group are obtained in a similar manner by condensing aliphatic aldehydes or ketones with benzene, *e g*

$$CH_3 \cdot CHO + 2HC_6H_5 = \underset{\text{Diphenyl ethane}}{CH_3 \cdot CH(C_6H_5)_2} + H_2O$$

This last reaction also permits the preparation of a number of diphenyl-methane derivatives, since, on the one hand, we may use different aldehydes and ketones and, on the other, numerous substitution products of benzene

Benzophenone, $C_6H_5 \cdot CO \cdot C_6H_5$, the ketone corresponding to diphenyl-methane, is formed when the latter is oxidised with chromic acid This compound and the secondary alcohol *benzhydrol*, $C_6H_5 \cdot CHOH \cdot C_6H_5$, have been described on p 434

p **Diamino diphenyl-methane**, $CH_2(C_6H_4NH_2)_2$, m p 87°, is obtained by heating aniline with *formaldehyde-aniline*, $C_6H_5N{:}CH_2$ (the condensation product of formaldehyde and aniline) In this reaction intramolecular change occurs

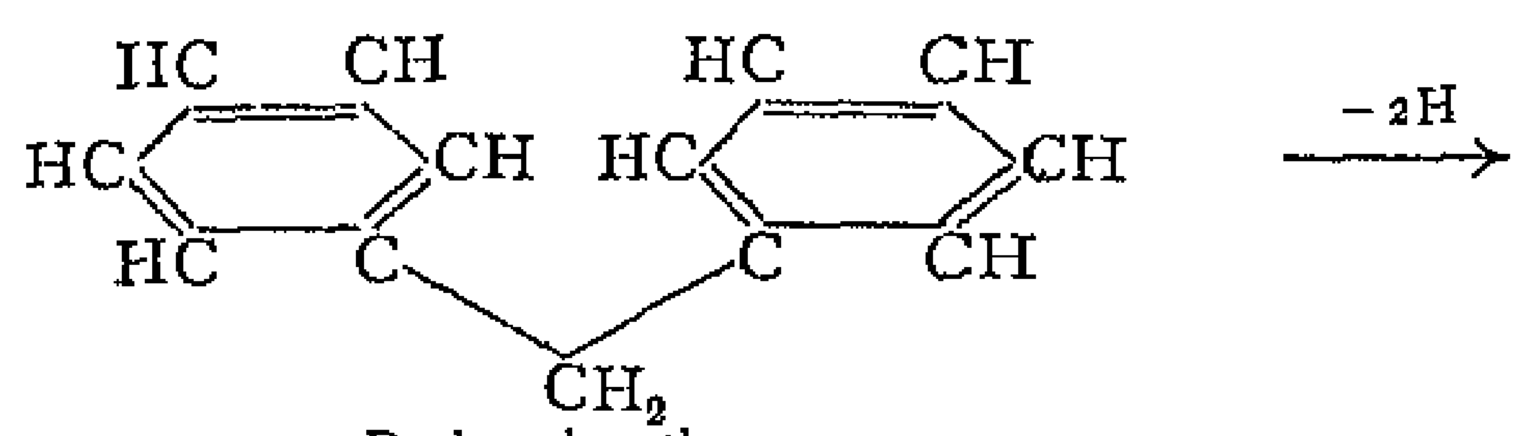
$$2C_6H_5NH_2 + HCHO = H_2N \cdot C_6H_4 \cdot CH_2 \cdot C_6H_4 \cdot NH_2 + H_2O$$

[1] Pummerer and Bittner, *Ber*, 1924, 57, 84

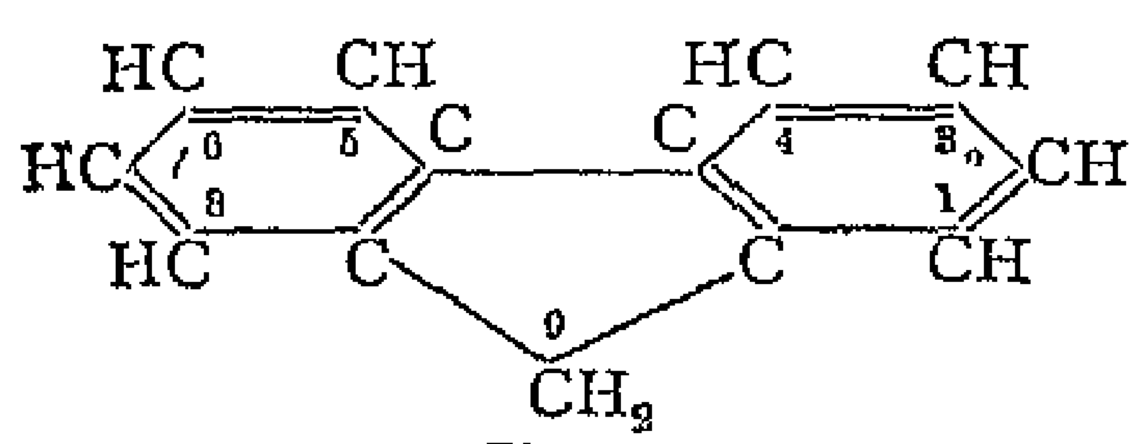
As will be seen later, this process is also used in the technical preparation of *New Fuchsine*

For *p*-**diamino-benzophenone** and its derivatives see p 435

A compound closely related to diphenyl-methane is *diphenylene-methane* or **fluorene**, which is obtained when diphenyl-methane is passed through a tube heated to redness



Diphenyl methane



Fluorene

Fluorene is present in coal tar, and may be obtained from diphenylene ketone or fluorenone (see p 493) by reduction with zinc dust or with hydriodic acid and phosphorus It melts at 113°, boils at 295°, and crystallises from alcohol in plates showing a violet fluorescence, from which it takes its name With picric acid it unites to form a red crystalline picrate, m p 81° *Owing to the arrangement of the double bonds in the molecule,*[1] *the hydrogen atoms of the CH_2-group in fluorene and similarly constituted hydrocarbons are very reactive*

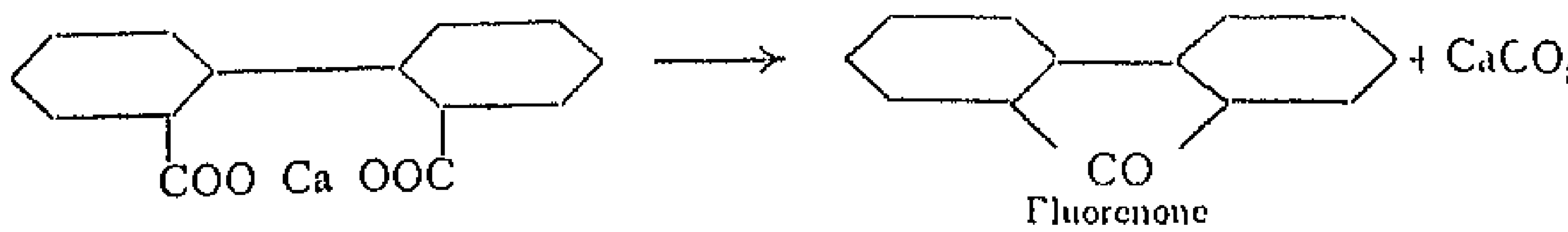
Thus fluorene condenses with oxalic ester, and with benzaldehyde In the latter case benzylidene-fluorene, $(C_6H_4)_2C \colon CH \cdot C_6H_5$, is formed The acidic nature of the CH_2-group is shown by the interaction of fluorene with caustic potash to give a solid *potassium compound*, $\begin{array}{l} C_6H_4 \\ | \\ C_6H_4 \end{array}\!\!\Big\rangle CHK$ By means of this compound the hydrocarbon can be isolated from coal tar and obtained in the pure state[2] On energetic oxidation fluorene yields phthalic acid

The direct preparation of fluorene derivatives from fluorene has recently been investigated by J Schmidt,[3] who has shown that the action of concentrated sulphuric acid on the hydrocarbon leads to the formation of 2 7-*fluorene-disulphonic acid*, which on fusion with potassium hydroxide gives 2 7 9 9-*tetrahydroxy-fluorene*

[1] J Thiele, *Ber*, 1900, 33, 851 *Ann*, 1906, 347, 249 W Wislicenus, *Ber*, 1900, 33, 771
[2] Weissgerber, *Ber*, 1901, 34, 1659 Weger and Döring, *Ber*, 1903, 36, 878 [3] J Schmidt and co-workers, *Ann*, 1909, 370, 1, 1912, 387, 147, 390, 210

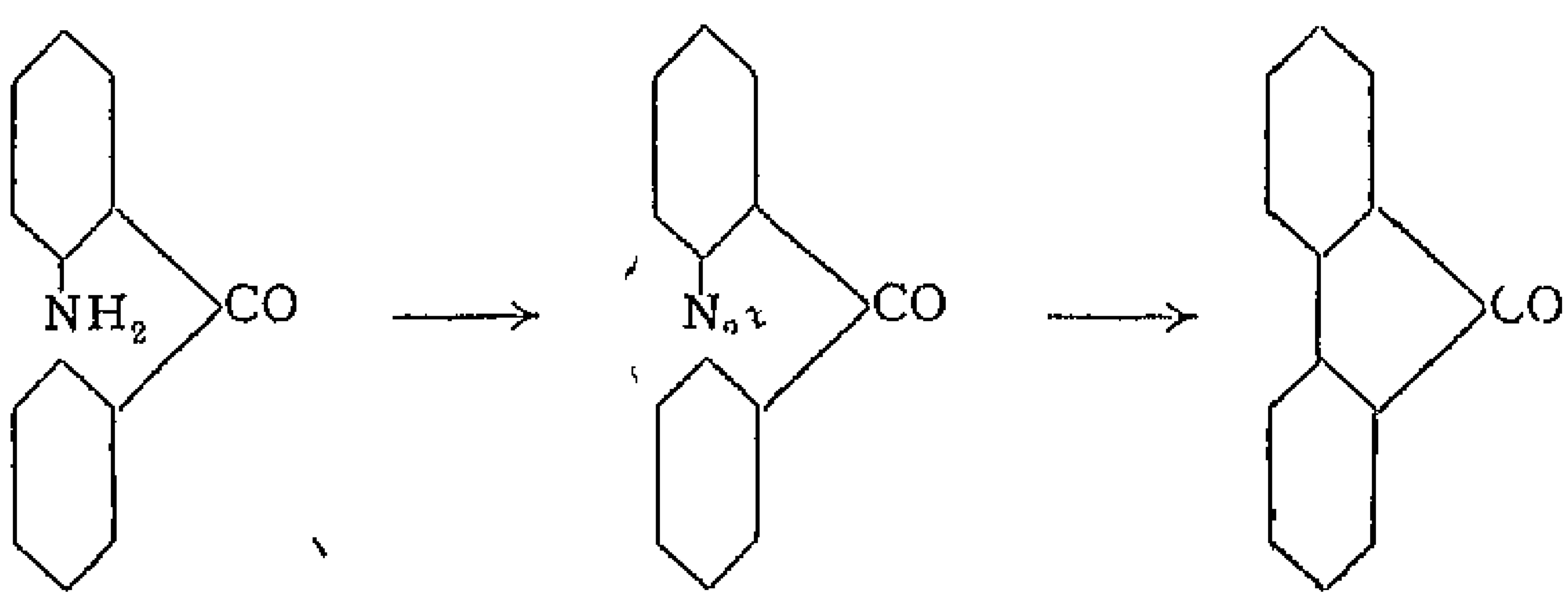
In the *formation of fluorene compounds* three methods are of special value

One of these depends on the conversion of appropriate derivatives of diphenic acid into derivatives of fluorenone, by elimination of carbon dioxide, *e g* the conversion of diphenic acid itself into fluorenone by the distillation of its calcium salt

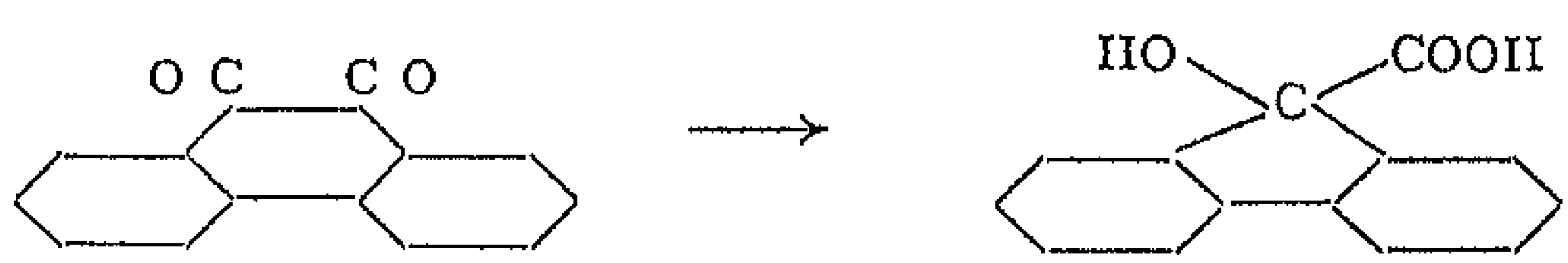


This method of preparation establishes the constitution of fluorenone and hence that of fluorene

A second method is based on the conversion of *o*-amino-benzophenone into *diphenylene-ketone* by diazotisation and removal of the diazo group

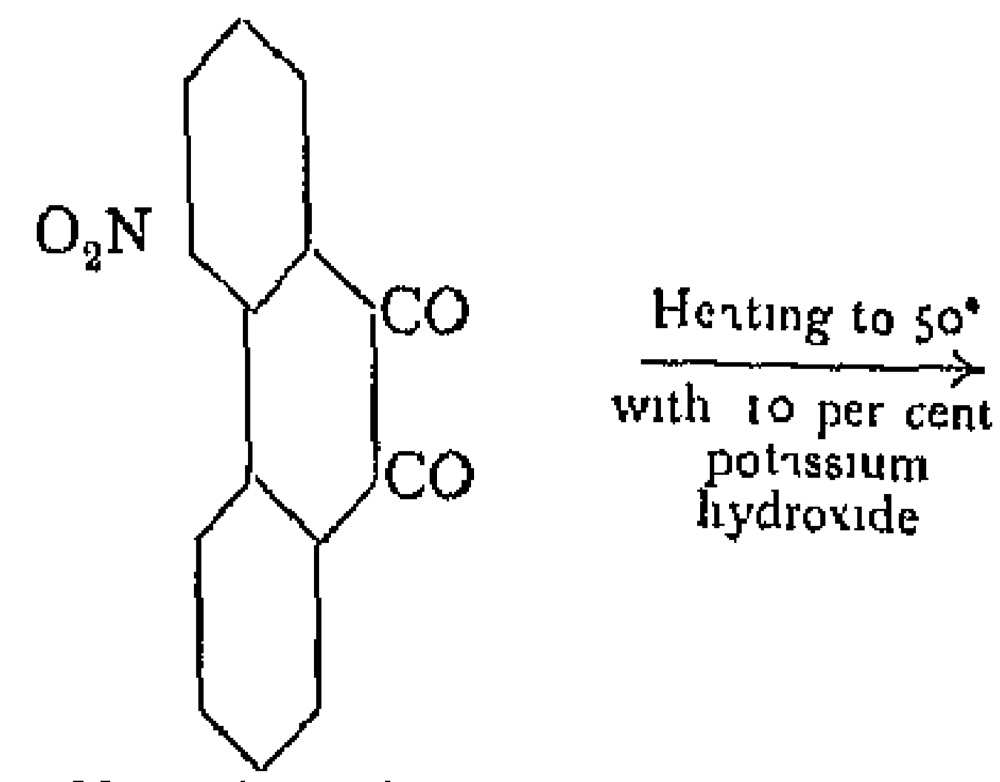


A third process starts from phenanthraquinone and its derivatives, which are described later When boiled with aqueous alkali, phenanthraquinone yields *diphenylene-glycollic acid* (9-hydroxy-fluorene-9-carboxylic acid)

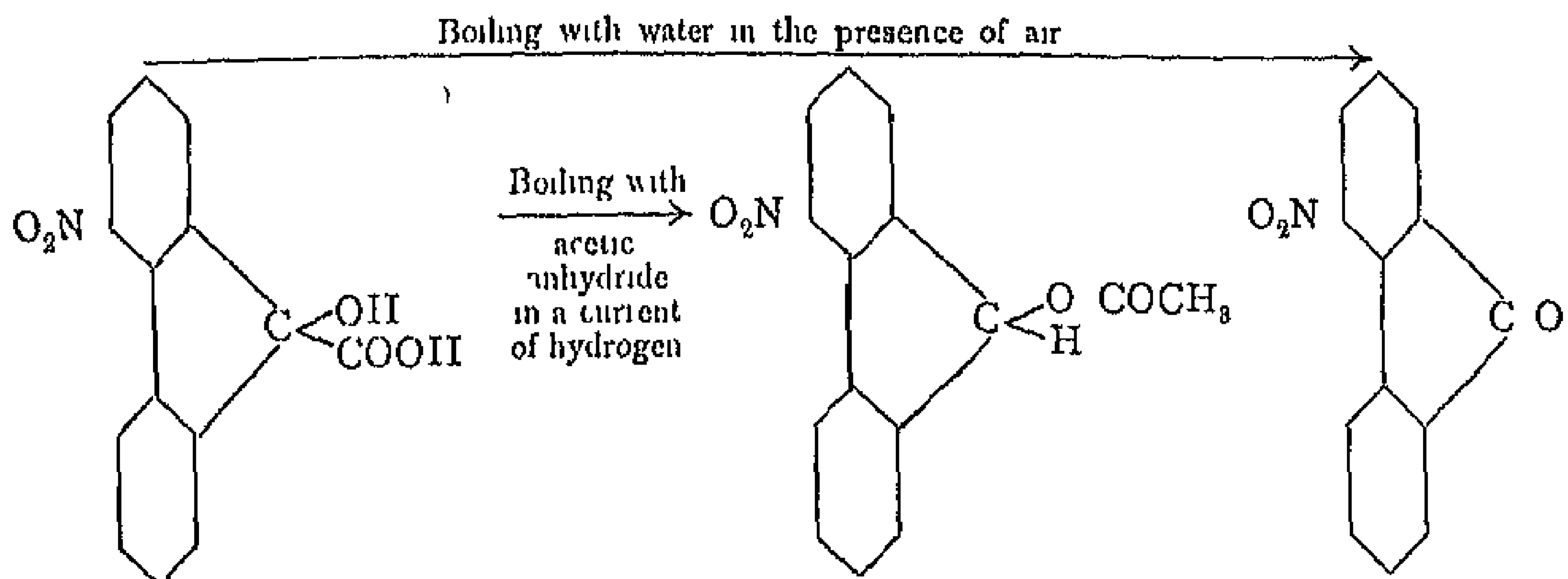


Substituted phenanthraquinones undergo a similar reaction to give the corresponding diphenylene-glycollic acids The latter can then be transformed into other derivatives of fluorene Most of them, when heated with acetic anhydride in the absence of air, lose carbon dioxide to form the acetyl derivative of the corresponding fluorenyl alcohol, when boiled with acetic anhydride, water, or alkalis, in the presence of air, oxidation occurs simultaneously with the production of a substituted fluorene ketone or fluorenone [1]

[1] J Schmidt and Bauer, *Ber*, 1905, 38, 3737.



4 Nitro phenanthraquinone



4 Nitro diphenylene glycollic acid Acetyl derivative of 4 nitro fluorenyl alcohol 4 Nitro-fluorenone

Fluorenone, or diphenylene ketone, is best prepared from fluorene by oxidation with sodium bichromate and glacial acetic acid It gives the usual reactions of ketones and is a yellow crystalline substance, m p 84° and b p 341° On reduction it yields *fluorenyl alcohol*, $(C_6H_4)_2CHOH$, which forms colourless crystals, m p 153°

Hexahydro fluorene has been isolated from a French gas coal by distillation under reduced pressure, and also by extraction with benzene[1] It boils at 110° to 120° under 10 mm, and at high temperatures loses hydrogen to form fluorene This change, which would also be expected to take place with other hydrogenated compounds, may be of general occurrence during the dry distillation of coal under ordinary pressure It therefore furnishes one, although not the only explanation of the presence of aromatic hydrocarbons in coal tar, and of hydrogen in coal gas

III —TRIPHENYL-METHANE GROUP

This group is of practical as well as theoretical importance On the one hand it includes a series of widely-used dye-stuffs—the rosanilines, aurines and phthaleins—and on the other it contains compounds

[1] A Pictet and Ramseyer, *Ber*, 1911, **44**, 2486

which have aroused very great interest in recent years owing to their unexpected properties

Triphenyl methane, $(C_6H_5)_3CH$, m p 92°, b p 358°, the parent substance of the whole group, is obtained by the following reactions

1 From the magnesium compound of triphenyl-chloro-methane by decomposition with water and acid[1] This is the most convenient method of preparing the hydrocarbon, since triphenyl-chloro-methane is easily obtained by treating carbon tetrachloride with benzene and aluminium chloride

$$ClCCl_3 + 3HC_6H_5 \xrightarrow{-3HCl} \underset{\text{Triphenyl chloro methane}}{ClC(C_6H_5)_3} \xrightarrow{Mg}$$

$$ClMgC(C_6H_5)_3 \xrightarrow{H_2O} HC(C_6H_5)_3 + Cl\ Mg\ OH$$

2 By the action of aluminium chloride on a mixture of benzal chloride and benzene, or of chloroform and benzene[2]

$$C_6H_5\ CHCl_2 + 2HC_6H_5 \xrightarrow{-2HCl} (C_6H_5)_3CH \xleftarrow{-3HCl} CHCl_3 + 3HC_6H_5$$

3 From benzaldehyde and benzene, or benzhydrol and benzene, under the influence of dehydrating agents such as zinc chloride

$$C_6H_5\ CHO + 2HC_6H_5 = (C_6H_5)_3CH + H_2O$$

By means of these reactions substituted derivatives of triphenyl-methane may also be prepared If, for example, in method 3, dimethylaniline is used in place of benzene, the leuco-base of malachite green is formed This important compound is described later

Triphenyl-methane is a white, crystalline substance, which is insoluble in water and cold alcohol, but readily dissolves in hot alcohol, ether and benzene From the last it crystallises in union with one molecule of the solvent When reduced with hydriodic acid and phosphorus it breaks up into benzene and toluene, and with oxidising agents it is converted into triphenyl-carbinol

According to Werner,[3] the triphenyl-methyl radical, $(C_6H_5)_3C$, has only a weakened valency bond at its disposal, and consequently the hydrogen atom with which it is united in triphenyl-methane can, under certain circumstances, take part in the formation of molecular compounds

Triphenyl-methane and its analogues are characterised by their ability to form such compounds, *e g*

$$(C_6H_5)_3CH + \underset{\text{Benzene}}{C_6H_6} \qquad (C_6H_5)_3CH + \underset{\text{Thiophene}}{C_4H_4S}$$

$$(C_6H_5)_3CH + \underset{\text{Pyrrole}}{C_4H_4\ NH} \qquad (C_6H_5)_3CH + \underset{\text{Aniline}}{C_6H_5\ NH_2}$$

[1] J Schmidlin, *Ber*, 1906, 39, 628, 1912, 45, 3188 [2] For the mechanism of the latter reaction see Norris and Lead, *Am C J*, 1901, 26, 499 Diphenyl-methane, anthracene and diphenylene phenyl methane are also formed [3] A Werner, *Ber*, 1906, 39, 1278

Substitution products of triphenyl-methane may be classified according to whether substitution has occurred in the methane residue, in the phenyl groups, or in both

Potassium triphenyl-methane, $(C_6H_5)_3CK$, is obtained by heating the hydrocarbon with potassium

Triphenyl-chloro-methane, $(C_6H_5)_3CCl$, m p 111°, has been mentioned on p 494 The chlorine atom in this compound is very mobile and easily detached With water, for example, hydrolysis occurs slowly in the cold and immediately on boiling, to form triphenyl-carbinol and hydrochloric acid With alcohol it reacts readily to give the *ethyl ether of triphenyl-carbinol*, m p 78°

$$(C_6H_5)_3C\cdot Cl + H_2O = (C_6H_5)_3C\cdot OH + HCl$$
$$(C_6H_5)_3CCl + HO\cdot C_2H_5 = (C_6H_5)_3C\cdot OC_2H_5 + HCl$$

It has been shown that the halogen atom of triphenyl-chloro-methane and similar halogen compounds possesses the power of attaching inorganic halides and other components to form highly coloured complexes,[1] such as $(C_6H_5)_3CCl\cdot AlCl_3$, $(C_6H_5)_3CCl\cdot SnCl_4$, $2(C_6H_5)_3CCl\cdot (HgCl_2)_3$ This peculiarity led Werner to the above assumption, that the three phenyl groups make such a demand on the affinity of the methane carbon atom that only a small surplus is left at the disposal of the fourth valency bond

Triphenyl Carbinol and the Basic Properties of Carbon

Triphenyl-carbinol, $(C_6H_5)_3C\cdot OH$, m p 163°, is readily prepared by the action of phenyl magnesium bromide on methyl benzoate or benzophenone[2] The experimental investigation of this compound has been of great interest in connection with the hypothesis of the basic character of carbon *In its chemical behaviour triphenyl-carbinol is a weak base* When treated in ethereal or benzene solution with dry hydrochloric acid gas, it is quantitatively converted into *triphenyl-chloro methane* The latter readily undergoes double decomposition with various silver salts, *e g* with silver chromate it forms yellowish-red *triphenyl chromate*, $[(C_6H_5)_3C]_2CrO_4$

By replacing the phenyl groups in triphenyl-carbinol with methoxy-phenyl groups, and especially with *p*-methoxyphenyl (anisyl) groups, Baeyer and Villiger succeeded in obtaining more strongly basic compounds which gave crystalline, highly-coloured salts even with dilute acids It was found that the effect depended largely on the position of the methoxyl group in the benzene ring, the increase of basicity being greatest in the *p*- and least in the *m*-position[3]

Salts of this type containing basic carbon are known as *carbonium salts* As will be shown later, the study of the salts of triphenyl-

[1] See also *J pr Ch*, 1921 (2), **103**, 1 [2] Ullmann, *Ber*, 1903, **36**, 406 Acree, *Ber*, 1904, **37**, 2755 [3] Baeyer and Villiger, *Ber*, 1902, **35**, 3020

carbinol and its substitution products has an immediate bearing on the constitution of triphenyl-methane dye-stuffs.

Triphenyl-carbinol not only possesses basic properties but its hydroxyl group is also chemically active in other ways, and can for example be directly replaced by alkoxyl groups. The other reactions of this compound, so far as they are known, appear to place it in an intermediate position between the alcohols and the acids in character, as may be seen from the following summary of its properties.

Triphenyl-carbinol extremely readily forms alkyl ethers with alcohols in the presence of dilute acids; alkalis, on the contrary, do not affect it. The ethyl ether is easily hydrolysed with dilute acids, but quite resistant towards alkalis. With zinc and glacial acetic acid the carbinol is readily reduced to triphenyl-methane. Its acetyl derivative, on being crystallised from alcohol, is converted quantitatively into the ethyl ether, and this with acetic anhydride or acetyl chloride again yields the acetyl compound. The carbinol itself can be acetylated with acetyl chloride, but not with acetic anhydride.

It has been shown by Walden that triphenyl-carbinol is a relatively good electrolyte. Triphenyl-methyl chloride and bromide conduct electricity even better, giving values approximating to those of the quaternary ammonium salts.

Another derivative of triphenyl-methane in which the substituent is in the methine group is **triphenyl-acetic acid**, $(C_6H_5)_3C \cdot COOH$. This is readily obtained[1] from the magnesium compound of triphenyl-methyl chloride by the action of dry carbon dioxide, followed by treatment with water and acids. It crystallises from glacial acetic acid in prisms, m.p. 263° to 264°.

Of the **diphenyl-tolyl-methanes**, $(C_6H_5)_2CH \cdot C_6H_4 \cdot CH_3$, in which substitution is in the benzene ring, the *m*-tolyl compound, m.p. 59°, having the methyl group in the meta-position to the methine carbon atom, has been prepared from leucaniline (see next section) by diazotisation and elimination of the diazo-groups. The *diphenyl-tolyl-carbinols*, which can be converted into the hydrocarbons by reduction, have recently been synthesised by means of Grignard's reaction.[2] *Diphenyl-p-tolyl-carbinol* was obtained in this manner from phenyl magnesium bromide and the methyl ester of *p*-toluic acid.

Constitution of Carbonium Salts

The *sulphates*,[3] *nitrates* and *perchlorates* of triaryl-methyls are without exception coloured in the crystalline state, and give in general coloured solutions. Some solvents, *e.g.* ether, form colourless solutions. In the coloured solutions and in the crystalline condition, the com-

[1] J. Schmidlin, *Ber.*, 1906, **39**, 634. See however Gillman and Zoellner, *J. Am. C. S.*, 1929, **51**, 5493. H. G. Rule and J. Bain, *J. C. S.*, **1930**, 1901. [2] Cf. *Ber.*, 1904, **37**, 656, 663, 1245. Also Acree, *ibid.*, 990. [3] Norris and Sanders, *Am. C. J.*, 1901, **25**, 54.

pounds are present as true salts, in colourless solutions they exist as esters

The solid triarymethyl *halides* are colourless, but form both colourless and coloured solutions In the latter an equilibrium exists between the two forms, as has been clearly shown by the optical investigations of Dilthey[1] Since the colourless chloride dissolves in strongly dissociating solvents to give a yellow solution which conducts electricity, it has been concluded that this compound also can exist in two modifications, one of which is colourless and unionised, and the other coloured and ionised

Baeyer proposed to describe ammonium, phosphonium, sulphonium, iodonium, oxonium and carbonium compounds as derivatives of *onium bases*

For the formulæ derived for dye-stuffs of the triphenyl-methane series from the above standpoint, see Baeyer (*Ber*, 1905, 38, 569)

A new conception of carbonium salts, based on their remarkable property of ionisation and general similarity to all other *onium* salts, has recently been advanced by Hantzsch[2] *Onium* halide salts derived from the elements nitrogen, phosphorus, oxygen and sulphur have been shown by Hantzsch to exist in two "chromo-isomeric" series, viz, true colourless halide salts of the complex formula, $(NR_4)X$, $(OR_3)X$, etc containing an indirect ionogenic or ionising linking of the halogen, and coloured pseudo salts of the type X N R_4, X O R_3, etc, so far only known in the case of iodides and bromides, containing a direct non-ionogenic union of the halogen According to this view there are also two isomeric series of carbonium salts

1 Yellow triphenyl carbonium halides or true salts

2 Colourless triphenyl-methyl halides or pseudo salts

On this hypothesis the carbon derivatives differ from those of N, P, O and S in that the true carbonium salts are coloured, whereas among the other *onium* compounds the pseudo-salts are the coloured forms

The close analogy between the two series of halide salts, $(C_6H_5)_3CX$, and the isomeric series of ammonium and oxonium halides is traced to a similarity in constitution Oxonium pseudo salts, for example, are regarded as normal derivatives of tetravalent oxygen (formula I), with halogen directly attached to oxygen The true oxonium halides, on the other hand, are complex salts in which oxygen functions as the central atom, the halogen being in ionic union (*ie*, indirect), with the -onium complex, and therefore in the outer sphere according to Werner's theory (II) Similarly, only the genuine triphenyl-methyl halides are derivatives of structurally normal tetravalent carbon, and owing to the direct linking of the halogens they are non-

[1] W Dilthey, *J pr Ch*, 1926 [2], 109, 273 [2] A Hantzsch, *Ber*, 1921, 54, 2573, 1930, 63, 1181 H E Fierz, *Helv Chim Acta*, 1921, 1, 221, *Ber*, 1922, 55, 429, 2013 K Brand, *J pr Ch*, 1925 [2], 109, 28

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[1] W. Dilthey, *J. pr. Ch.*, 1925 [2], 109, 273. [2] A. Hantzsch, *Ber.*, 1921, 54, 2573; 1930, 63, 1181. H. F. Fierz, *Helv. Chim. Acta*, 1921, 4, 221; *Ber.*, 1922, 55, 129, 2043. K. Brand, *J. pr. Ch.*, 1925 [2], 109, 28.

electrolytes and therefore pseudo carbonium salts (III). The true triphenyl carbonium salts are electrolytes and must be considered to be complex salts analogous to the true oxonium salts. In these compounds the methane carbon functions as the central atom and is only directly united to the three phenyl groups, thus forming the complex cation, the halogen or acidic radical is situated in the outer sphere, and is in indirect or ionogenic union (IV).

$$\text{Pseudo salts}\quad \text{I}\quad \begin{array}{c} \mathrm{R} \\ \mathrm{R\;O\;X} \\ \mathrm{R} \end{array} \qquad\qquad \text{III}\quad \begin{array}{c} \mathrm{C_6H_5} \\ \mathrm{C_6H_5\;C\;X} \\ \mathrm{C_6H_5} \end{array}$$

$$\text{True salts}\quad \text{II}\quad \left(\mathrm{R\;O}\begin{array}{l} \diagup \mathrm{R} \\ \diagdown \mathrm{R} \end{array}\right)\mathrm{X} \qquad\qquad \text{IV}\quad \left(\mathrm{C_6H_5\;C}\begin{array}{l} \diagup \mathrm{C_6H_5} \\ \diagdown \mathrm{C_6H_5} \end{array}\right)\mathrm{X}$$

The theory of carbonium salts may be summarised as follows. Tetravalent carbon resembles tetravalent oxygen and sulphur in its ability to function in the cation of an *onium* salt when linked directly to three hydrocarbon radicals. Pseudo salts built up from a group of this kind and an acidic atom or complex may undergo rearrangement in such a manner that the acidic group changes to indirect union in the outer sphere, and in this state functions as an anion. The complex formula for triphenyl carbonium salts, $[\mathrm{C\;Ar_3}]\mathrm{X}$, given above, is supported by data for optical absorption and electrical conductivity, as well as by a number of purely chemical reactions.

Triphenyl-methane Dye-stuffs

From the colourless hydrocarbon, triphenyl-methane, the leuco-compounds of dye-stuffs may be derived by replacing hydrogen in the benzene nuclei by certain chromophoric groups of atoms. Chief among the latter are the amino-group, in which hydrogen may also be substituted by alkyl radicals, and the hydroxyl group. In addition to the derivatives discussed on p. 444, in connection with phthalic anhydride, we have the two following series:

1. The Rosaniline group, derived from amino-triphenyl-methane.
2. The Aurine group, derived from hydroxy-triphenyl-methane.

Constitution of the Triphenyl-methane Dye-stuffs.—The relationship of these compounds to triphenyl methane, which is discussed below, was first shown in 1878 by *E.* and *O. Fischer*. Since then the greatest advance on the theoretical side has been the introduction of the quinonoid formula by *Nietzki*, but opinions as to the finer structural details are almost as numerous as the researches on the di- and triphenyl-methane dye-stuffs themselves.

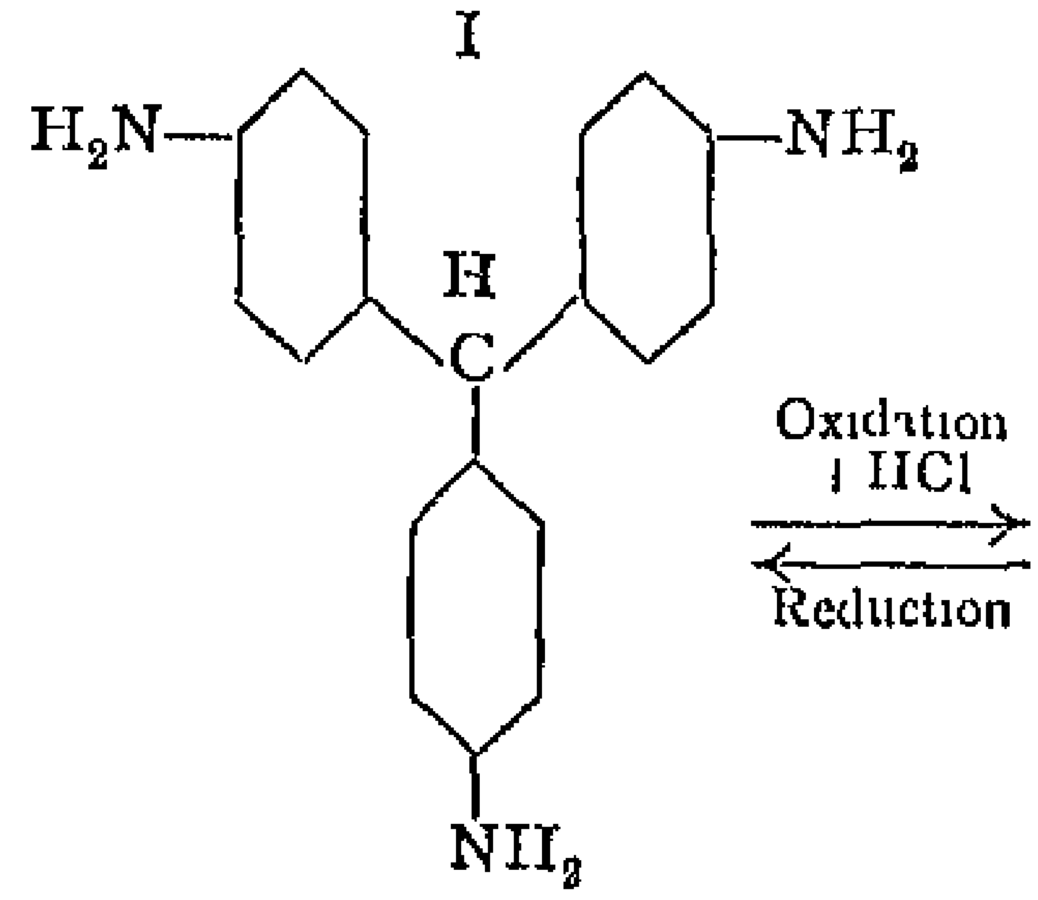
If three amino-groups are introduced into the three benzene nuclei of triphenyl-methane, in the *p*-positions to the methine group,

a compound of the structure I is obtained, known as *p*-triamino-triphenyl-methane, or more commonly as *para-leucaniline*.

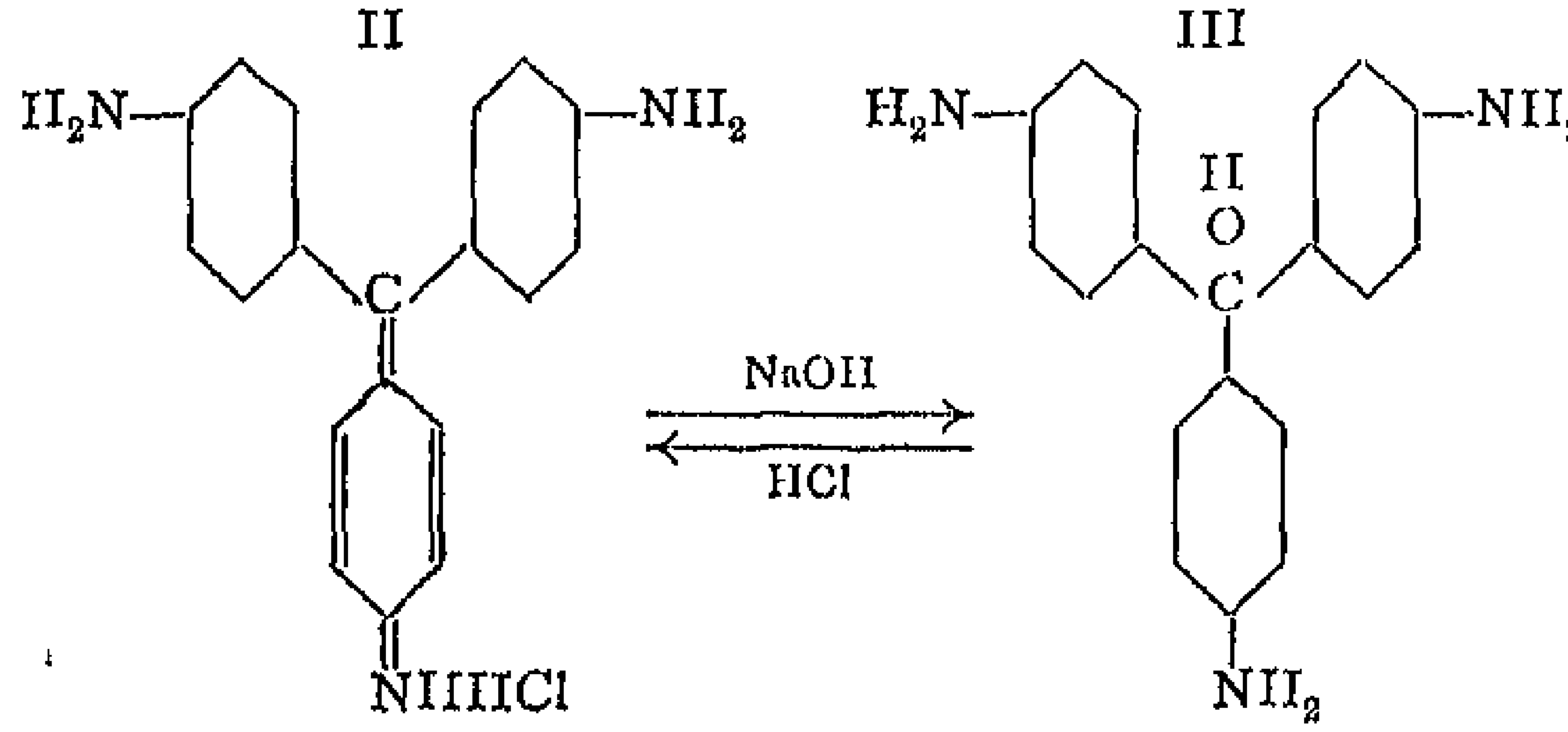
Leuco bases or **leuco compounds** are the colourless compounds obtained by the reduction of dye-stuffs. On oxidation they are again converted into dye-stuffs. The use of these terms is not limited to the triphenyl-methane series, but is common to the indigo and other groups of dyes.

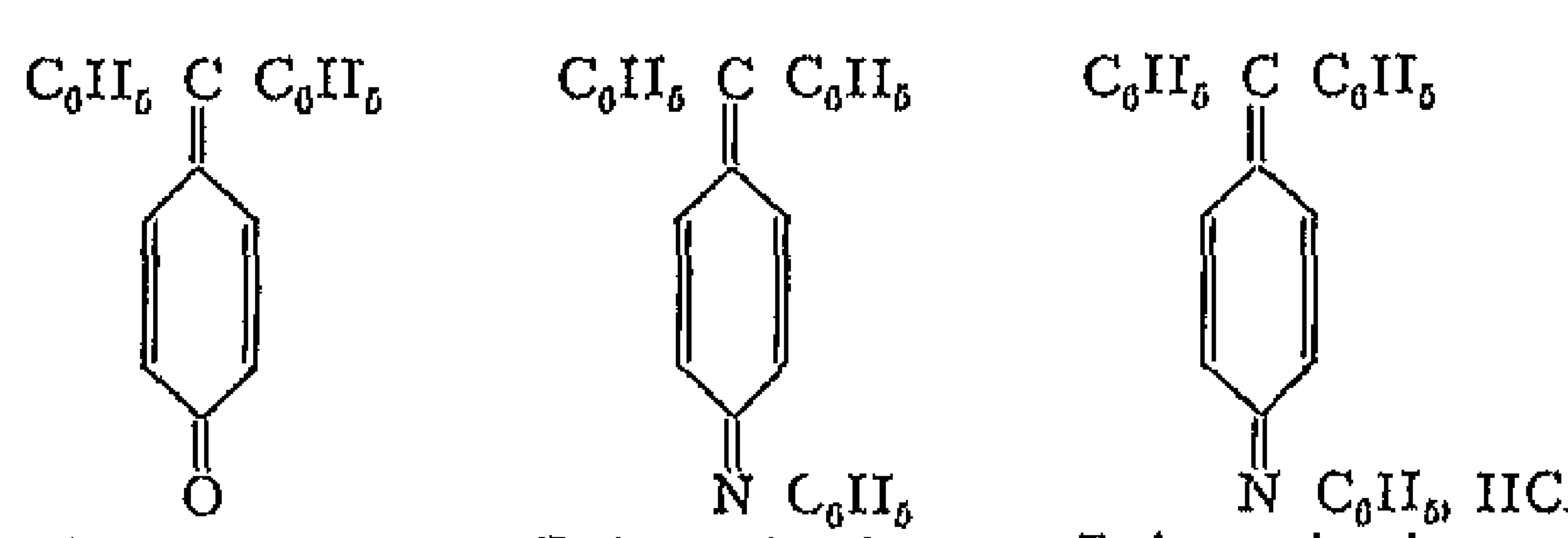
When *p*-triamino-triphenyl-methane is treated with oxidising agents, a dye base is obtained which is only stable in the form of its salts, *e.g.* as the hydrochloride *pararosaniline hydrochloride* (II). On being liberated from its salts the free base changes more or

I



II III





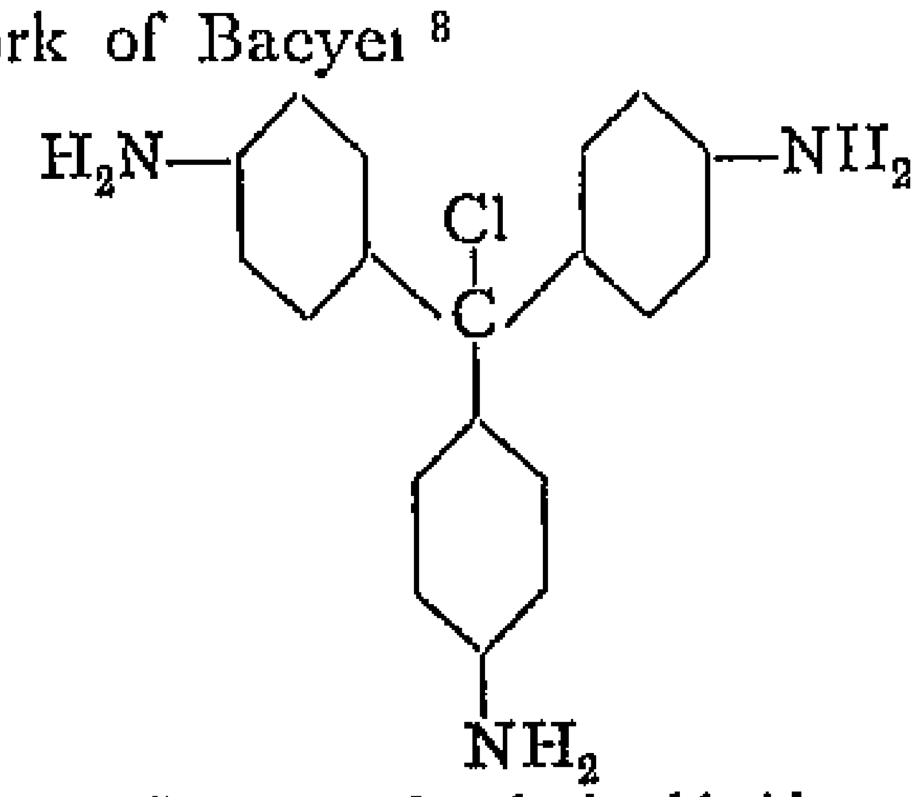
Diphenyl quino methane or fuchsone — Fuchsone phenylimine — Fuchsone phenyl imonium chloride[1]

[1] Imonium indicates a compound of the ammonium type, in which a double C linking (imino group) is also present.

less rapidly into colourless *triamino-triphenyl-carbinol* (III) Since the dye-stuffs are in many ways similar to the quinonimine dyes, they are considered by most chemists to possess the quinonoid structure, as represented in formula II

Stable forms of this type of colour base have been discovered[1] among phenyl quinonimine derivatives by Baeyer and Villiger The parent substance of this group of compounds may be considered to be diphenyl-quino-methane, for which the name *fuchsone* has been suggested, thus enabling members of this group to be named systematically

The probability of the quinonoid formula, as applied to salts of triphenyl-methane dyes, has been considerably strengthened by recent research,[2] and this formulation will be adopted in the following pages For a long time, however, the structure suggested in 1880 by Rosenstiehl, representing the salts as esters of a carbinol (see formula below), was regarded as being as probable as the quinone formula and was supported by the work of Baeyer[3]



Para-rosaniline hydrochloride
or para fuchsine
(*Rosenstiehl's formula*)

It must be admitted that the newer conceptions, which are more or less based upon the older Rosenstiehl formula, can be supported by a considerable body of evidence According to Fierz, Dilthey and others[4] the triaryl-methylium salts $[Ar_3C]X$ discussed on pp 497, 498 are to be regarded as the chromogens, from which dye-stuffs of the triphenyl-methane series are derived by the replacement of hydrogen atoms by auxochrome groups, such as OH, NH_2, NMe_2, etc

The nature of the colour bases of triphenyl-methane dye-stuffs will be discussed more fully at the end of this chapter

[1] Baeyer and Villiger (*Ber*, 1904, 37, 597, 2848) obtained the quinonoid anhydride of *p* aminotriphenyl carbinol, *fuchsonimine*, $\left[\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>C=C_6H_4=NH\right]_2$, in a colourless, crystalline dimolecular state by the interaction of phenyl magnesium bromide and *p* amino benzophenone Many of the triphenyl methane colour bases exist in two forms, a colourless carbinol and a coloured quinonoid modification Baeyer and Villiger, 1902, 35, 715 Noelting and Philipp, *Ber*, 1908, 41, 579 [2] *Cf* Wieland, Popper and Seefried, *Ber*, 1922, 55, 1816 [3] Baeyer, *Ber*, 1906, 38, 569 [4] H Fierz and H Koechlin, *Helv Chim Acta*, 1919, I, 210, W Dilthey, *J pr Ch*, 1925, [2] 109, 273, W Madelung, *J pr Ch*, [2], 1926, 111, 100, K Brand, *ibid*, 1925, 109, 28, R Wizinger, *Ber*, 1927, 60, 1377

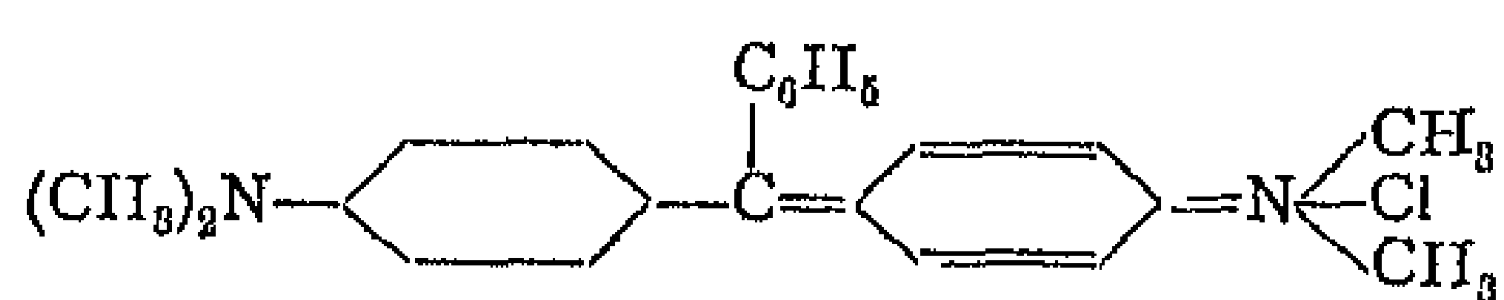
1 Rosaniline Dye stuffs

Malachite green, *Victoria green* When benzaldehyde is heated on the water-bath with dimethylaniline in the presence of condensing agents such as hydrochloric acid, sulphuric acid or zinc chloride, there is formed tetramethyl-di-*p*-amino triphenyl-methane or *leuco-malachite green* In this reaction the hydrogen atoms in the *p*-position to the $N(CH_3)_2$ groups unite with the aldehydic oxygen atom, with elimination of water The leuco-base is obtained in colourless leaflets or prisms

$$C_6H_5\ CHO + \begin{matrix} H\ C_6H_4\ N(CH_3)_2 \\ H\ C_6H_4\ N(CH_3)_2 \end{matrix} = C_6H_5{-}CH\begin{matrix} \diagup C_6H_4\ N(CH_3)_2 \\ \diagdown C_6H_4\ N(CH_3)_2 \end{matrix} + H_2O$$

Leuco base of malachite green

When the hydrochloride of the leuco-base is oxidised, malachite green is obtained This is usually carried out in dilute solution by means of lead peroxide in the presence of a little acetic acid



Quinonoid formula for malachite green

The compound is most conveniently isolated from solution in the form of the zinc double salt, $3(C_{23}H_{25}N_2Cl)$, $2ZnCl_2$, H_2O, by precipitation with zinc chloride and common salt, or the carbinol base may be precipitated with sodium carbonate, and converted into the oxalate by treatment with oxalic acid

The zinc double salt or the oxalate is placed on the market in the form of green crystals having a metallic sheen Malachite green dyes wool, silk, jute, leather and tannined cotton a green colour, which is not very fast to light

Tetramethyl diamino triphenyl carbinol,

$$C_6H_5\ C(OH)\begin{matrix} \diagup C_6H_4N(CH_3)_2 \\ \diagdown C_6H_4N(CH_3)_2 \end{matrix}$$

is produced by the action of alkalis on malachite green It may be synthesised by the interaction of 2 mols of dimethylamino-phenyl magnesium bromide with 1 mol benzoic ester, and forms colourless crystals, m p 132°.

Among the various dyes of this type used in industry the following may be mentioned [1]

[1] For the influence of substitution on the colour of malachite green, see Noelting and Gerlinger, *Ber*, 1906, 39, 2041

Brilliant green, *Guignet's green*, is the ethyl compound corresponding to malachite green, obtained by condensing diethylaniline with benzaldehyde

Patent blue, the *o-p*-disulphonic acid of *m*-hydroxy-malachite green, is prepared by condensing *m*-nitrobenzaldehyde with dimethylaniline, replacing NO_2 by OH by way of the diazo compound, followed by sulphonation and oxidation It is an important dye-stuff which dyes wool a very fast greenish-blue colour and is stable towards alkali

Triamino triphenyl carbinols and their Derivatives

The true rosaniline dye-stuffs are derived from p_3-triamino-triphenyl-carbinol (formula III, p 499) and p_3-triamino-diphenyl-*m*-tolyl-carbinol

$$\begin{matrix} NH_2\ C_6H_4 \\ NH_2\ C_6H_4 \end{matrix}\!\!>\!C\!<\!\begin{matrix} OH \\ C_6H_3\!<\!\begin{matrix} CH_3 \\ NH_2 \end{matrix} \end{matrix}$$

When treated with an equivalent of hydrochloric or acetic acid these compounds lose a molecule of water and form salts of the type illustrated on p 499, which are valuable dyes Owing to their preparation from crude *p*-toluidine, the dyes derived from p_3-triamino-triphenyl carbinol were originally distinguished as para compounds (*e g*, para-rosaniline, para-rosolic acid), and this inconvenient nomenclature is still in use

Para rosaniline, $C_{19}H_{19}N_3O$ (constitution, see p 498), is prepared by oxidising a mixture of *p*-toluidine (1 mol) and aniline (2 mols) Among the numerous oxidising agents available for this purpose, arsenic acid (the older process) or nitrobenzene is generally used It is supposed that the methyl group of *p*-toluidine is first oxidised to the aldehyde stage, and the *p* amino-benzaldehyde so formed condenses with aniline as in the malachite green preparation (p 501) Hence the "methane carbon atom" of para-rosaniline has its origin in the methyl group of *p*-toluidine[1]

$$\begin{matrix} H_2N\ C_6H_5 \\ H_2N\ C_6H_5 \end{matrix} + H_3C\ C_6H_4\ NH_2 + 3O$$

2 mols aniline + 1 mol *p* toluidine

$$= \begin{matrix} H_2N\ C_6H_4 \\ H_2N\ C_6H_4 \end{matrix}\!\!>\!C\!<\!\begin{matrix} C_6H_4\ NH_2 \\ OH \end{matrix} + 2H_2O$$

Para rosaniline

The colourless carbinol base—which is triacidic and more strongly basic than ammonia—unites with one equivalent of an acid with loss of water to form red dyes Simultaneously the molecule undergoes rearrangement into the quinonoid structure (possibly, however, the carbinol ester type persists, see pp 499 and 500) Hydrochloric acid

[1] On examining this reaction it is clear that pure aniline alone can yield neither para rosaniline nor rosaniline on oxidation (it actually gives products of the induline type) In this case the group required for the formation of the "methane carbon" is wanting

yields para-rosaniline hydrochloride or **para fuchsine**, which is a constituent of technical fuchsine. On reduction with zinc dust and hydrochloric acid this salt is converted into *para-leucaniline* or p-*triamino-triphenyl-methane* (colourless needles, m.p. 148°), from which para-rosaniline is easily regenerated by oxidation.

Rosaniline, $C_{20}H_{21}N_3O$, is a homologue of para-rosaniline and is obtained by the above condensation when 1 mol. aniline is replaced by 1 mol. *o*-toluidine, *i.e.*, when an equimolecular mixture of aniline, *o*-toluidine and *p*-toluidine is oxidised.

$$\begin{array}{l} H_2N\cdot C_6H_5 \\ {\begin{array}{l}H_2N\\H_3C\end{array}}{>}C_6H_4 \end{array} + H_3C\cdot C_6H_4\cdot NH_2 + 3O$$

$$= \begin{array}{l} H_2N\cdot C_6H_4 \\ {\begin{array}{l}H_2N\\H_3C\end{array}}{>}C_6H_3 \end{array}{>}C{<}\begin{array}{l} C_6H_4\cdot NH_2 \\ OH \end{array} + 2H_2O$$

Rosaniline,
triamino diphenyl tolyl carbinol

Rosaniline, like para-rosaniline, is a colourless triacidic base, which unites with one equivalent of an acid to form coloured salts of the colour base, a molecule of water being set free. The salt containing one molecular proportion of hydrochloric acid is known as **fuchsine**. In the solid state the latter consists of green crystals with a metallic lustre. It dissolves in water, giving a deep reddish-purple colour. The solution dyes silk and wool directly, and cotton after having been mordanted with tannin and potassium hydrogen tartrate. But the red colours so obtained are not fast to light. On reduction, rosaniline gives *leucaniline*, $\begin{array}{l}NH_2\\CH_3\end{array}{>}C_6H_3-CH(C_6H_4\cdot NH_2)_2$, m.p. 100°.

Rosaniline also forms acid salts such as $C_{20}H_{20}N_3Cl + 3HCl$, which gives a yellowish brown solution. On the addition of much water these dissociate into the neutral salts and free acid.

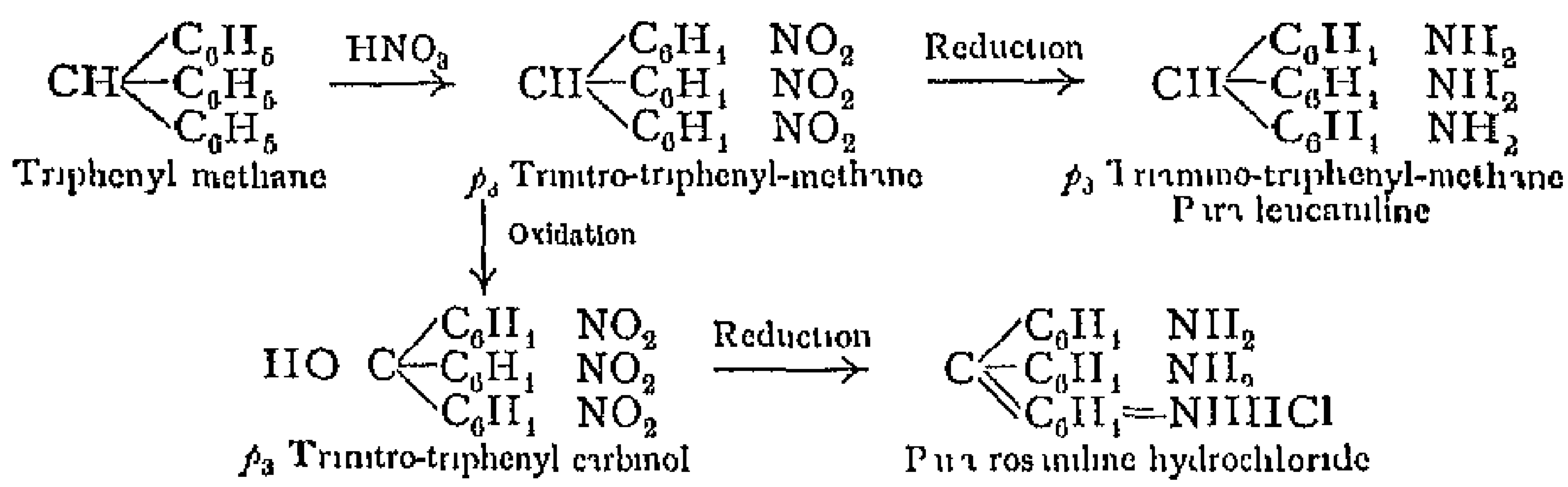
The relationship of para-fuchsine and fuchsine to triphenyl-methane was explained in 1878 by E. and O. Fischer.[1] Para-fuchsine (para-rosaniline hydrochloride) was reduced to the hydrochloride of para-leucaniline, and the latter converted by way of the diazonium salt into triphenyl-methane.

$$C{\Large<}\begin{array}{l} C_6H_4\cdot NH_2 \\ C_6H_4\cdot NH_2 \\ C_6H_4{=}NH\cdot HCl \end{array} \longrightarrow CH{\Large<}\begin{array}{l} C_6H_4\cdot NH_2\cdot HCl \\ C_6H_4\cdot NH_2\cdot HCl \\ C_6H_4\cdot NH_2\cdot HCl \end{array} \longrightarrow CH{\Large<}\begin{array}{l} C_6H_5 \\ C_6H_5 \\ C_6H_5 \end{array}$$

In addition, triphenyl-methane was synthesised from benzene and chloroform in the presence of aluminium chloride, and converted by

[1] *Ann.*, **194**, 242. F. Fischer and Jennings, *Ber.*, 1893, **26**, 2220.

nitration into p_3-trinitro-triphenyl-methane, from which para-leucaniline and para-rosaniline were obtained as follows —



The first series of changes was also carried through with rosaniline, yielding *m*-tolyl-diphenyl methane

Finally, the assumption that the three amino-groups in rosaniline and para-rosaniline occupied the para-positions was also proved beyond doubt by other reactions

Nuclear-substituted Fuchsines

In addition to the methods described above, a number of other processes for the preparation of fuchsine dye-stuffs have been developed One of these involves the condensation of formaldehyde with aniline to give formaldehyde-aniline, $C_6H_5-N=CH_2$, which on further treatment with aniline is converted with intramolecular rearrangement into diamino diphenyl-methane (p 490) When this base is heated with aniline and an oxidising agent (nitrobenzene), a hydrogen atom of the CH_2-group is replaced by an aminophenyl group, with the production of para-fuchsine By employing substituted anilines in place of aniline itself this method may be used for the preparation of substituted fuchsines

New Fuchsine, $C_{22}H_{23}N_3HCl$, containing three *o*-toluidine groups in place of the three aniline residues, is very readily obtained in the above way It dyes a bluish-red and is more soluble in water than fuchsine

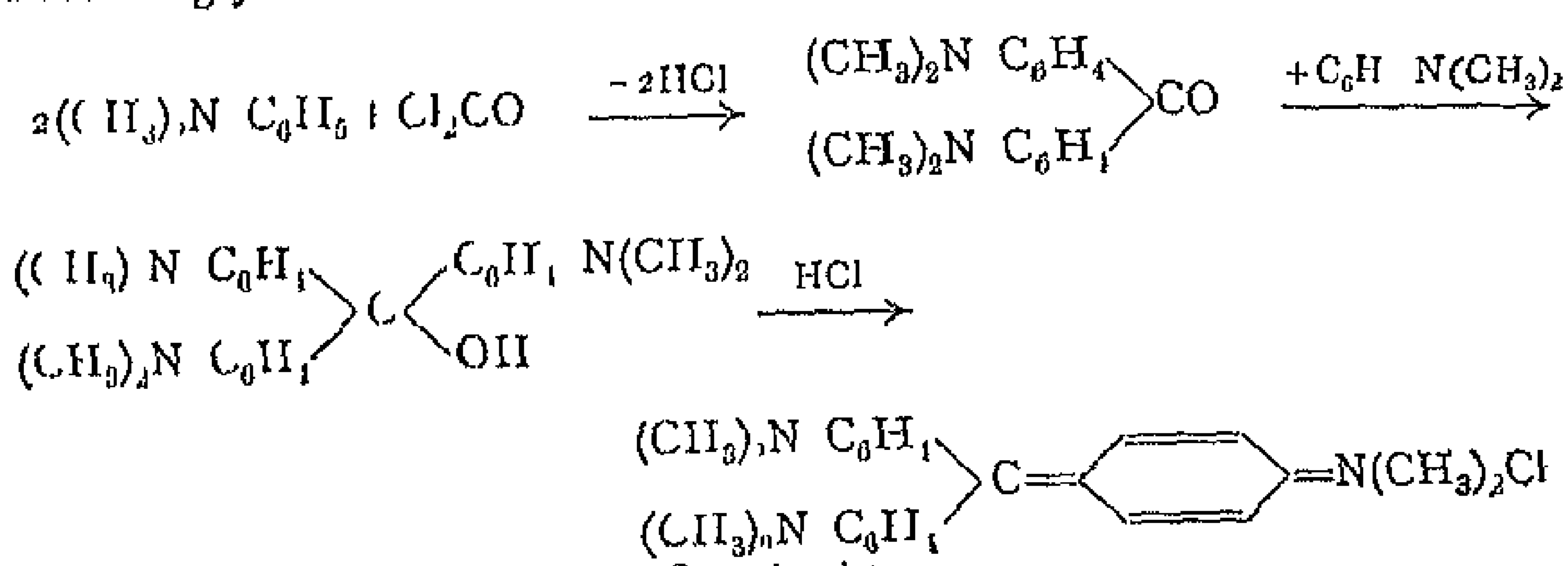
Acid Fuchsine, *acid magenta*, $C_{20}H_{17}N_3(SO_2\ ONa)_2$, is a disulphonic derivative of fuchsine, prepared by heating rosaniline with fuming sulphuric acid at 120° It dyes wool and silk in weak acid bath, thus enabling fuchsine to be used as an acid dye

Methylated and Phenylated Derivatives

When the hydrogen atoms of the NH_2-groups in rosaniline and para-rosaniline are replaced by methyl or ethyl groups, the red colour of the dye is changed to violet The tendency towards blue becomes

more pronounced as the number of alkyl groups increases. At first these compounds were obtained by alkylating rosaniline with the aid of methyl or ethyl iodide, and later by use of methyl alcohol and hydrochloric acid in place of the more expensive methyl iodide. Recently dimethyl-aniline (prepared by heating aniline with methyl alcohol and hydrochloric or sulphuric acid at 200°) has been used as starting material and oxidised directly to alkylated para-rosanilines, usually by means of cupric salts. In this manner **methyl violet** is obtained, consisting of a variable mixture of the hydrochlorides of tetra-, penta- and hexamethyl para-rosanilines. It is an iridescent green resinous mass, which dissolves in water to give a beautiful violet solution. If hydrogen is substituted by benzyl groups ($C_6H_5 \cdot CH_2$—), instead of methyl groups, a bluer shade is obtained (*benzyl violet*).

Crystal violet is the hydrochloride of pure hexamethyl para-rosaniline. It is prepared by the interaction of phosgene and dimethyl-aniline to form tetramethyl-diamino-benzophenone (Michler's ketone, p. 435), and condensing the latter with dimethyl-aniline in the presence of phosphorus chloride or aluminium chloride. It crystallises exceedingly well.



Crystal violet

An interesting method of forming crystal violet is as follows (*Ber*, 36, 4296). On mixing an ethereal solution of dimethylamino phenyl magnesium bromide with an ethereal solution of Michler's ketone, a yellowish brown precipitate of the additive magnesium compound is first obtained (equation I). On acidification with hydrochloric acid this yields hexamethyl triamino-triphenyl carbinol (equation II), which changes into the hydrochloride of crystal violet.

I. $$(CH_3)_2N \cdot C_6H_4 \cdot CO \cdot C_6H_4 \cdot N(CH_3)_2 + Br \cdot Mg \cdot C_6H_4 \cdot N(CH_3)_2 = \begin{matrix}(CH_3)_2N \cdot C_6H_4 \\ BrMgO\end{matrix} > C < \begin{matrix}C_6H_4 \cdot N(CH_3)_2 \\ C_6H_4 \cdot N(CH_3)_2\end{matrix}$$

II. $$\begin{matrix}(CH_3)_2N \cdot C_6H_4 \\ (CH_3)_2N \cdot C_6H_4\end{matrix} > C < \begin{matrix}C_6H_4 \cdot N(CH_3)_2 \\ OMgBr\end{matrix} + HCl = [(CH_3)_2N \cdot C_6H_4]_3C \cdot OH + MgClBr$$

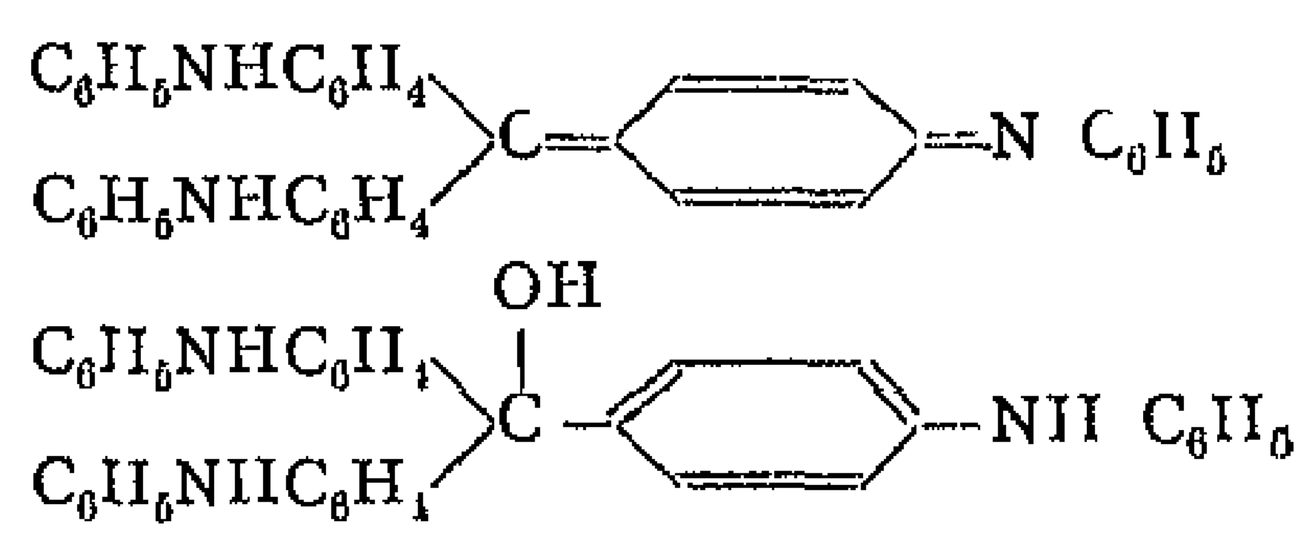
Pure blue dye-stuffs may be obtained from rosaniline by replacing the amino-hydrogen atoms by phenyl or naphthyl groups.

Aniline blue, *triphenyl-para-rosaniline hydrochloride*, is prepared by heating rosaniline with a large excess of toluidine-free aniline and benzoic acid to 180°, when ammonia is liberated On treating the product with hydrochloric acid the dye crystallises out It can also be obtained by the oxidation of diphenylamine The dye is very sparingly soluble in water, but more soluble in alcohol, hence it is sometimes termed "spirit blue" Sulphonic derivatives of this compound are soluble in water and are more often used than the parent substance The sodium salt of the monosulphonic acid, known as **alkali blue**, is used especially for dyeing wool, and the sodium salts of the di- and trisulphonic acids, **water blue**, for dyeing cotton

Diphenylaminofuchsone-phenylimine, the imine base of aniline blue (formula I), has been prepared by heating trianisyl-carbinol with benzoic acid and aniline, and subsequently decomposing the benzoate of the dye with sodium hydroxide under special conditions[1] The compound is a black crystalline powder, m p 237° to 238°, which readily adds on water to form triphenyl-para-rosaniline (formula II) On reduction it yields the leuco-base, and with acids gives the corresponding dye-salts

I

II



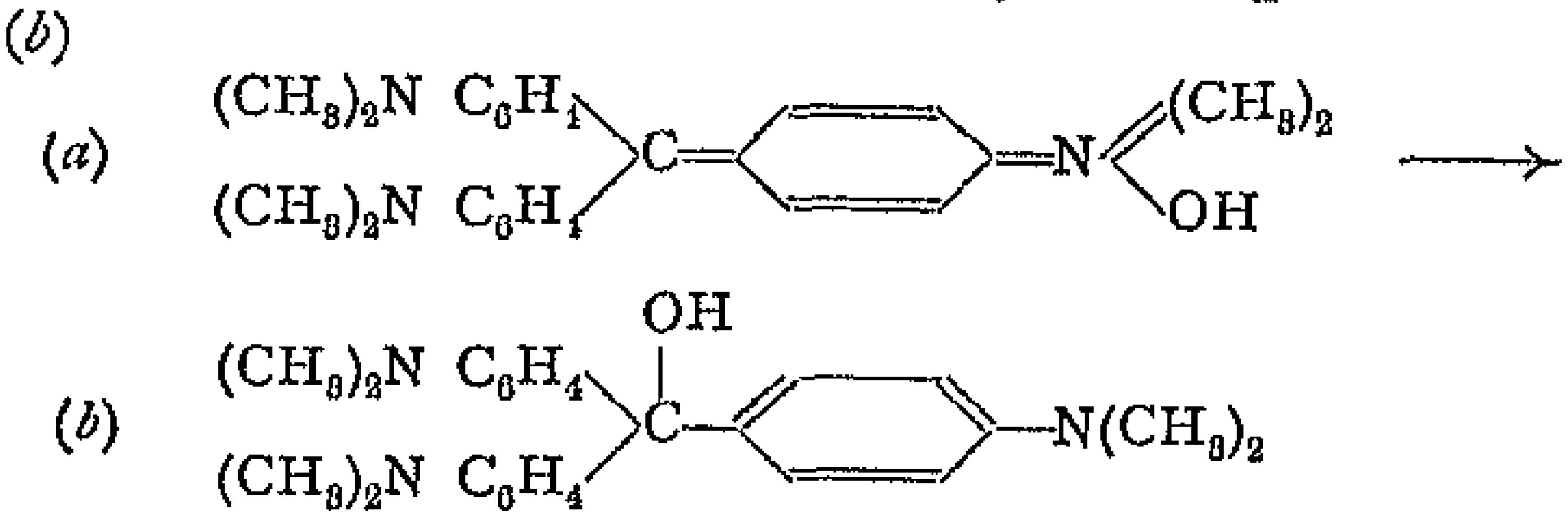
Constitution of the Rosaniline Dye bases

The views at present held regarding the constitution of triphenylmethane salts have already been discussed on pp 497-500, and the following paragraphs deal with the nature of the dye *bases* which give rise to the salts In this connection Hantzsch[2] has drawn a number of conclusions from a physico-chemical examination of the conductivity of the system *dye-salt* + 1 *NaOH*

When crystal violet (the hydrochloride of hexamethyl-triaminotriphenylmethane) is treated in solution with one equivalent of alkali, the coloured solution first obtained is strongly alkaline and conducts the electric current In time, however, it becomes colourless, and finally both alkalinity and conductivity disappear together It appears therefore that, immediately after the addition of an equivalent of alkali to crystal violet, the actual base of structure (*a*) is present in solution,

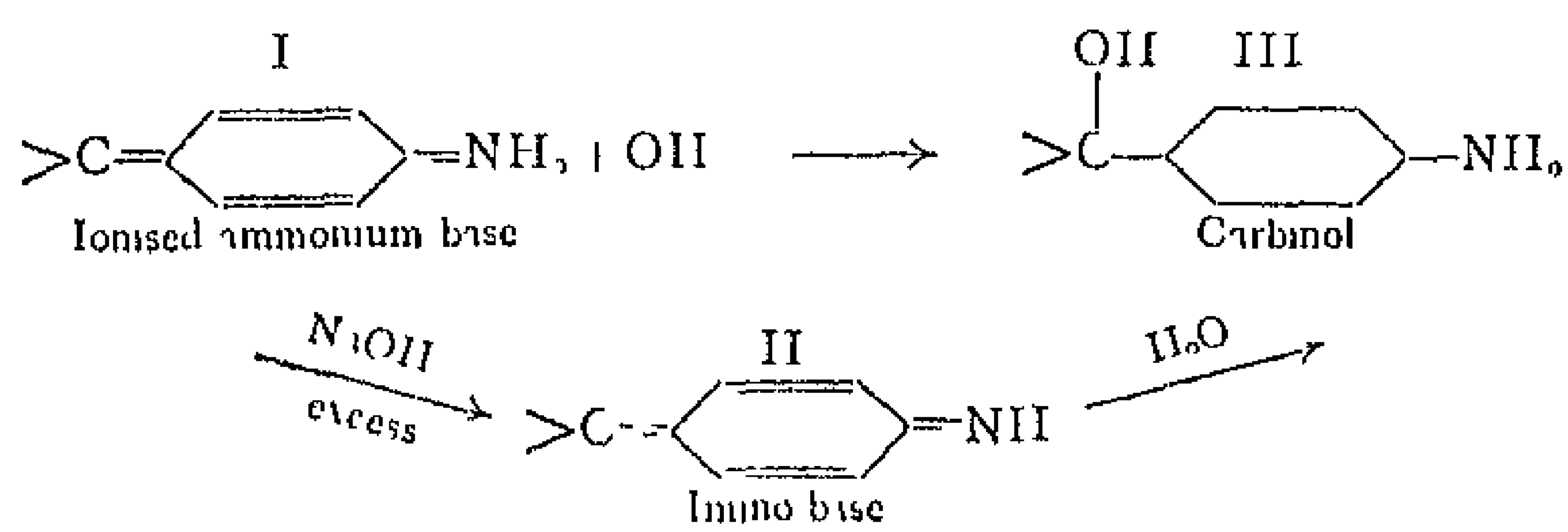
[1] Baeyer and Villiger, *Ber*, 1904, 37, 2870 [2] Hantzsch, *Ber*, 1900, 33, 278, 752; *Ber*, 1904, 37, 3434

and that this slowly isomerises to the dye-base (pseudo-base) of formula (*b*)



Similar results are obtained with other bases of triphenyl methane dye-stuffs, and the conclusions arrived at by Hantzsch may be summarised as follows

The true primary bases of the dye-salts of this series are ammonium hydroxide derivatives of the same colour as the salts They cannot be isolated in the solid state but exist only in dilute aqueous solution, *i e*, in the almost completely ionised condition[1] (formula I)



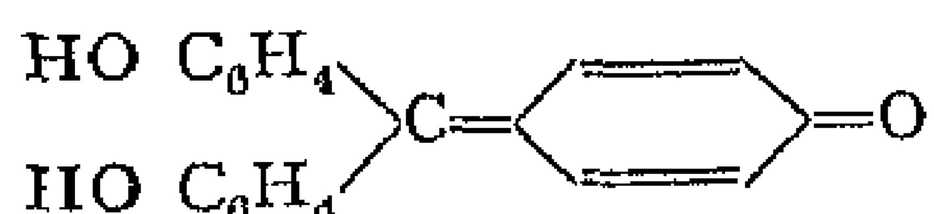
Even in the dissociated state these dye-bases slowly undergo molecular rearrangement with variable but always measurable velocity to form the pseudo-bases or carbinols (formula III) When the salt of a dye-base such as fuchsine, which still contains hydrogen attached to nitrogen, is treated in aqueous solution with *excess* of sodium hydroxide, an anhydro-base of different colour is precipitated (formula II) This can be extracted with indifferent solvents Fuchsine, for example, yields a brown compound known as *Homolka's base*[2] These anhydrides are related to the primary dye-bases as ammonia is to ammonium hydrate The imino-base is therefore not to be considered as the actual base of fuchsine, but rather as its anhydride With acids it is instantly converted into salts of the dye base

2 Aurines, Rosolic Acid Dyes

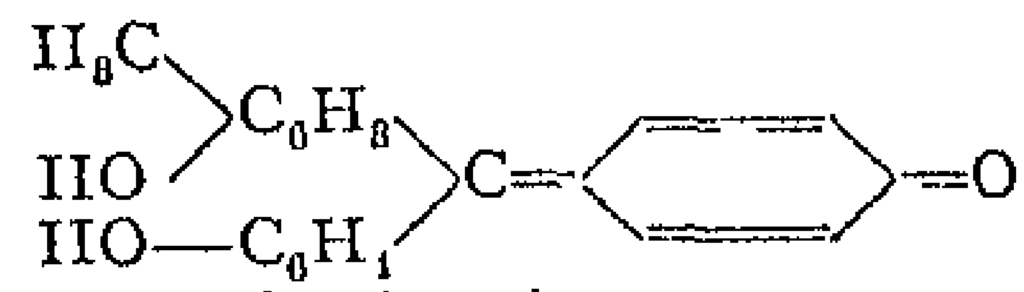
Compounds of this class possess a constitution similar to that of the true rosaniline dyes, although the nitrogen has been replaced by oxygen groups, they therefore bear the same relationship to phenol as

[1] These formulæ only show that part of the molecule undergoing change [2] This base was first obtained from fuchsine by Homolka and is formulated according to type II above as $(NH_2C_6H_4)_2C \cdot C_6H_4 \cdot NH$ (Baeyer and Villiger, *Ber*, 1905, 88, 579)

the rosanilines bear to aniline. Hence they are not basic but weakly acidic dyes, which are, however, of much less value than those of the rosaniline series, since they are difficult to attach to the fabric. They are chiefly employed in the form of lakes in the paper and wall-paper industries. In these compounds the quinonoid structure is assumed so readily—even in the absence of mineral acid—that the corresponding carbinols are unknown.



Aurine, para rosolic acid



Rosolic acid

Aurine, *para-rosolic acid*, may be obtained in the pure state from para-rosaniline by diazotisation and boiling the diazonium salt with water, when NH_2 is replaced by OH. Technically it is prepared by heating phenol with sulphuric acid and oxalic acid (the latter furnishing the "methane carbon atom"). It forms dark red rhombic crystals or red needles with a greenish lustre, dissolves in alkali to a fuchsine red solution, and has also weakly basic properties since it unites with acids. When heated to 150° with aqueous ammonia it yields para-rosaniline, and with nascent hydrogen it is reduced to *leucaurine*, trihydroxy-triphenyl-methane, $CH(C_6H_4 \cdot OH)_3$. The latter is a colourless, crystalline compound which turns red in air or with oxidising agents, owing to the formation of aurine. Trianisyl-carbinol, the trimethyl ether of the carbinol corresponding to aurine, has already been mentioned on p. 495.

Rosolic acid, the quinonoid anhydride of p_3-trihydroxy-diphenyl-*m*-tolyl carbinol (formula, see above), is formed when the diazo-compound of rosaniline is boiled with water, or when a mixture of phenol and cresol is heated with arsenic acid and sulphuric acid (the methyl group of cresol provides the "methane carbon"). It forms crystals of greenish lustre which are insoluble in water and dissolve to a red solution in alkalis. With reducing agents rosolic acid is converted into *leuco rosolic acid*, trihydroxy-diphenyl-tolylmethane, $(HOC_6H_4)_2CH \cdot C_6H_3(CH_3) \cdot OH$. When heated with water, rosolic acid breaks up into *p*-dihydroxyphenyl-tolyl ketone and phenol.

The *phthaleins*, which may be regarded as carboxy-derivatives of triphenyl-methane, have already been discussed in connection with phthalic anhydride.

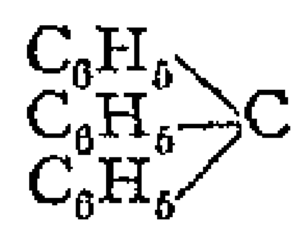
Triphenyl-Methyl and Trivalent Carbon

The problem of the valency of carbon has assumed a new aspect in the light of the recent researches of Gomberg[1] (*cf* p. 16).

[1] Gomberg, *J Am C S*, 1900, 22, 757; 1901, 23, 317; 1913, 35, 446; 1914, 36, 1144; 1919, 41, 1655; 1922, 44, 1810; 1923, 45, 190, 207. See also monograph by J. Schmidlin *Das Triphenylmethyl*, published by Enke, Stuttgart.

By treating triphenyl-methyl chloride in an atmosphere of CO_2 with zinc, silver or mercury, Gomberg obtained a strongly unsaturated hydrocarbon which he termed *triphenyl-methyl* and formulated according to I

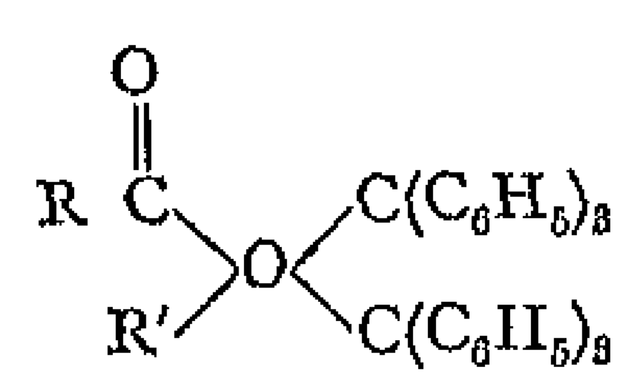
I



II

On this view of its structure triphenyl-methyl may be described as the first compound to be discovered containing trivalent carbon By similar methods a number of analogous compounds have been prepared [1]

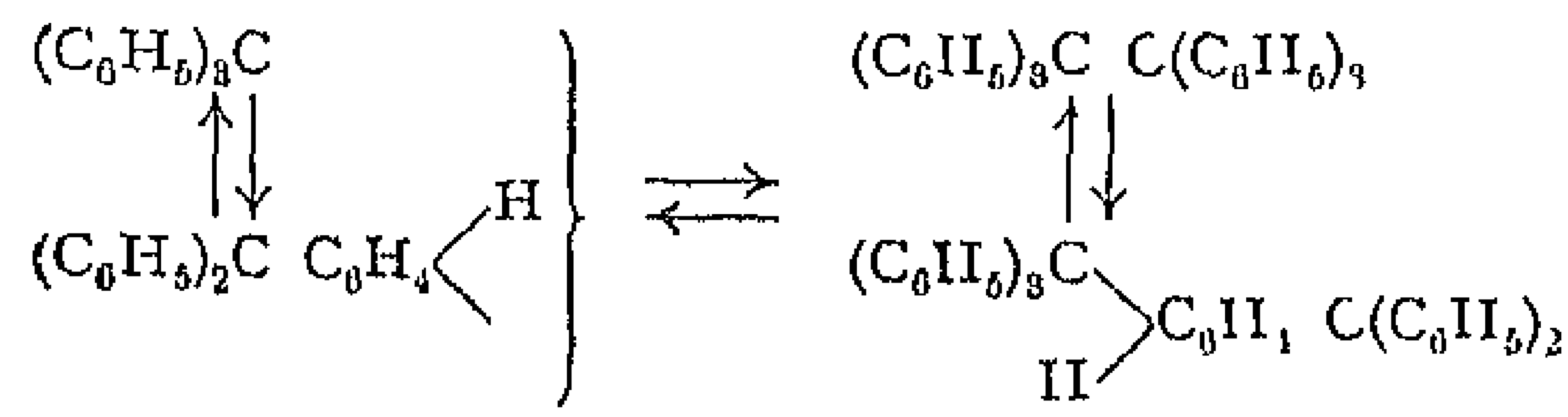
This hydrocarbon has aroused great interest owing to its unusual properties The colourless solid compound becomes yellow on solution in organic solvents, in which state a colourless dimolecular form (possibly hexaphenyl ethane) exists in equilibrium with a smaller proportion of the yellow monomolecular triphenyl-methyl The unsaturated properties of the compound are illustrated in its behaviour towards oxygen and the halogens, as well as in the formation of additive compounds with various classes of organic substances In the air it immediately absorbs oxygen with the production of a *peroxide*, $(C_6H_5)_3C\ O\ O\ C(C_6H_5)_3$, m p 185° A solution of iodine is immediately decolorised by triphenyl-methyl to form *triphenyl-methyl iodide*, $(C_6H_5)_3CI$, m p 132° With ether a crystalline compound of the composition $2(C_6H_5)_3C+(C_2H_5)_2O$ is obtained, in which oxygen appears to be tetravalent Esters also combine with triphenyl-methyl, giving compounds which probably possess the annexed structure Ketones, aromatic and unsaturated aliphatic hydrocarbons, etc, also give addition products, that with amylene, for example, having the formula $[(C_6H_5)_3C]_2+C_5H_{10}$ The experimental evidence so far available shows that when triphenyl-methyl combines with another substance, each valency of the latter which is brought into play invariably takes up one $(C_6H_5)_3C$-complex, regardless of the stability of the resulting product Amylene and all aromatic hydrocarbons, as well as ethers, esters and ketones, take up in a uniform manner two triphenyl-methyl groups per molecule



Although formula I above is in good agreement with the chemical behaviour of triphenyl-methyl, it is not supported by the fact that the compound can exist in the dimolecular state in solution Hence it has met with a certain amount of criticism [2] and other suggestions have

[1] Pentaphenyl ethyl, Schlenk and Mark, *Ber*, 1922, 55 [*B*], 2285, 2299 For other compounds see Schlenk, *Ann*, 1909, 368, 303, 372, 1 J Schmidlin, *Ber*, 1912, 45, 3171 Schlenk and Bornhardt, *Ber*, 1913, 46, 1482 [2] Norris and Sanders, *J Am C S*, 1901, 25, 54, 117, 1903, 29, 129 Kehrmann, *Ber*, 1901, 34, 3815, 35, 622 Heintschel, *Ber*, 36, 320, 579 Ullmann and Borsum, *Ber*, 35, 2877 Tschitschibabin, *Ber*, 1904, 37, 4709, 38, 771 Jacobson, *Ber*, 38, 196 Hantzsch, *Ber*, 1906, 39, 2478

been advanced, more particularly in connection with the structure of the dimolecular form. Among the latter should be noted formula II (p. 509), suggested by Jacobson,[1] according to which the hydrocarbon is of quinonoid type, *viz.*, 1-diphenylmethylene-4-triphenylmethyl-cyclohexadiene-(2 : 5). While this constitution does not completely explain the chemical properties of triphenyl-methyl, it supplies a satisfactory reason for the dimolecular state and avoids any assumption of trivalent carbon. Thus it is seen that a number of facts can be quoted for and against both of the formulæ I and II. Gomberg[2] concludes that the properties of triphenyl-methyl and its analogues are provisionally best expressed by assuming an equilibrium of the following type between the mono- and dimolecular compounds in benzenoid and quinonoid forms:

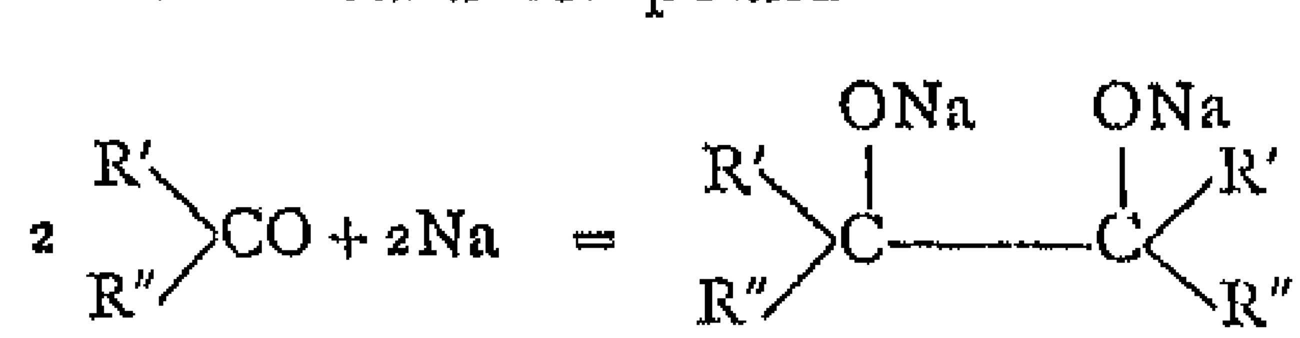


Triphenyl-methyl undoubtedly occurs in two modifications in solution, a coloured monomolecular form being in equilibrium with a colourless dimolecular form. On the other hand, tribiphenyl-methyl, $(C_6H_5 \cdot C_6H_4)_3C$, occurs only in a purple monomolecular form, and the investigation of this compound has gone far to establish the existence of trivalent carbon.

Metallic Ketyls.—Another group of compounds containing trivalent carbon has been discovered by Schlenk in the metallic ketyls,[3] of the general formula shown below. They are formed by the action of alkali metals on ketones, and are characterised by intense colour and great sensitiveness to oxygen. Trivalent carbon therefore appears to betray itself in its strong chromophoric influence. In general, the interaction of an alkali metal and a ketone falls into one of the three following classes:

1. Where an enolic form can occur a metallic compound is produced with evolution of hydrogen, as in the case of acetone, which reacts as the enol $CH_2 : C(OH) \cdot CH_3$.

2. The alkali metal may combine without evolution of hydrogen to form a saturated dimolecular compound:



[1] See Note 2 on p. 509. [2] Gomberg, *Ber.*, 1913, 46, 225. [3] Schlenk and Thal, *Ber.*, 1913, 46, 2840.

3. The alkali metal may combine directly to yield a metallic ketyl:

$$\begin{matrix} R' \\ R'' \end{matrix}\!\!>CO + Na = \begin{matrix} R' \\ R'' \end{matrix}\!\!>C\diagdown_{ONa}$$

Sodium ketyl

IV.—TETRAPHENYL METHANE GROUP

Tetraphenyl-methane, $(C_6H_5)_4C$, can be prepared from triphenyl-carbinol. The latter, on heating with aniline hydrochloride, yields the hydrochloride of *p-amino-tetraphenyl-methane*, and from the free base (m.p. 245°) the amino-group is eliminated by the diazo reaction:

$$(C_6H_5)_3C\cdot OH \longrightarrow (C_6H_5)_3C—C_6H_4\cdot NH_2 \longrightarrow (C_6H_5)_3C—C_6H_5$$

It has also been shown by Gomberg[1] that tetraphenyl-methane is readily obtained by the action of phenyl magnesium bromide on triphenyl-methyl chloride:

$$(C_6H_5)_3C\cdot Cl + C_6H_5MgBr = (C_6H_5)_4C + MgBrCl$$

It forms colourless crystals, m.p. 282° and b.p. 431°.

If triphenyl-carbinol is heated with phenol, instead of with aniline, the resulting product is *p-hydroxy-tetraphenyl-methane*, m.p. 282°:

$$C(C_6H_5)_3\cdot OH + C_6H_5OH = C(C_6H_5)_3(C_6H_4\cdot OH) + H_2O$$

V.—DIBENZYL OR DIPHENYL ETHANE GROUP

Dibenzyl, *s-diphenyl-ethane*, $C_6H_5\cdot CH_2\cdot CH_2\cdot C_6H_5$, can be prepared by the action of copper or sodium on benzyl chloride,

$$C_6H_5CH_2\cdot Cl + Na_2 + Cl\cdot CH_2C_6H_5 = C_6H_5CH_2\cdot CH_2C_6H_5 + 2NaCl$$

by the oxidation of toluene with potassium persulphate,

$$2C_6H_5\cdot CH_3 + K_2S_2O_8 = C_6H_5\cdot CH_2\cdot CH_2\cdot C_6H_5 + K_2SO_4 + H_2SO_4$$

and by the reduction of stilbene with sodium and alcohol:

$$C_6H_5\cdot CH:CH\cdot C_6H_5 + 2H = C_6H_5\cdot CH_2\cdot CH_2\cdot C_6H_5$$

Homologues of dibenzyl may be obtained by similar methods, e.g., *o*-, *m*- and *p*-xylene on oxidation with potassium persulphate yield o_2-, m_2-, and p_2-dimethyl-dibenzyl respectively.

Dibenzyl forms a glistening white crystalline mass. It melts at 52°, and boils at 284°.

Stilbene, *s-diphenyl-ethylene*, $C_6H_5\cdot CH:CH\cdot C_6H_5$, has been known a long time and is formed in a great many reactions. It is best pre-

[1] Gomberg, *Ber.*, 1906, 39, 1461. Freund, *Ber.*, 39, 2237.

pared by the interaction of benzaldehyde and benzyl magnesium chloride, the carbinol first produced immediately parting with water

$$C_6H_5\cdot CH:O + Mg\begin{cases}CH_2\cdot C_6H_5\\ Br\end{cases} \longrightarrow C_6H_5\cdot CH\begin{cases}CH_2\cdot C_6H_5\\ OMgBr\end{cases} \longrightarrow$$

$$C_6H_5\cdot CH\begin{cases}CH_2\cdot C_6H_5\\ OH\end{cases} \xrightarrow{-H_2O} C_6H_5\cdot CH:CH\cdot C_6H_5$$

By this method a great variety of substituted stilbenes have also been obtained, *e.g.*, *a-phenyl-stilbene*, or *triphenyl-ethylene*, $(C_6H_5)_2C:CH\cdot C_6H_5$, which melts at 68° and boils at 221° under 14 mm.

Another method of preparing stilbene consists in heating an alkaline solution of phenyl-nitromethane

$$2C_6H_5\cdot CH:NO\cdot ONa = C_6H_5\cdot CH:CH\cdot C_6H_5 + 2NaNO_2$$

This may be much more readily effected by starting from the sodium compound of phenyl-nitro-acetonitrile, which is easily obtained from ethyl nitrate and benzyl cyanide

$$\begin{aligned}&2C_6H_5C(CN):NO\cdot ONa + 4NaOH + 2H_2O\\ &\quad = C_6H_5\cdot CH:CH\cdot C_6H_5 + 2Na_2CO_3 + 2NH_3 + 2NaNO_2\end{aligned}$$

Stilbene crystallises in lustrous plates or prisms, m.p. 124° and b.p. 306°. It yields dibenzyl on reduction, and readily adds on halogens and hydrogen halides, *e.g.* with bromine it forms stilbene dibromide, $C_6H_5\cdot CHBr\cdot CHBr\cdot C_6H_5$.

p-**Nitrostilbene** is produced by the interaction of benzaldehyde and nitrophenyl-acetic acid in the presence of piperidine[1]

$$\begin{aligned}&C_6H_5\cdot CHO + H_2C(COOH)\cdot C_6H_4\cdot NO_2 \rightarrow C_6H_5\cdot CH:C(COOH)\cdot C_6H_4\cdot NO_2 \rightarrow\\ &\qquad C_6H_5\cdot CH:CH\cdot C_6H_4\cdot NO_2\end{aligned}$$

It forms yellow needles, m.p. 155° and exists also in a labile modification,[2] m.p. 64°. With stannous chloride it is easily reduced to colourless *p*-**amino-stilbene**.

p$_2$-**Diamino-stilbene**, $NH_2\cdot C_6H_4\cdot CH:CH\cdot C_6H_4\cdot NH_2$, and its disulphonic acid are used in the preparation of substantive azo dyes. They are obtained from *p*-nitrotoluene or its sulphonic acid. When *p*-nitrotoluene sulphonic acid is boiled with sodium hydroxide it yields *p*-azoxy-stilbene disulphonic acid, from which on reduction with zinc dust and alkali is obtained diamino-stilbene disulphonic acid.

Tolane, *diphenyl-acetylene*, $C_6H_5\cdot C\equiv C\cdot C_6H_5$, is prepared from the above-mentioned stilbene dibromide by boiling with alcoholic potash

$$C_6H_5CHBr\cdot CHBr\cdot C_6H_5 + 2KOH = C_6H_5\cdot C:C\cdot C_6H_5 + 2KBr + 2H_2O$$

[1] P. Pfeiffer and Sergiewskaja, *Ber.*, 1911, 44, 1107. For stilbene *o*-carboxylic acids, see Pfeiffer and Matton, *ibid.*, p. 1113. [2] R. Stoermer and Oehlert, *Ber.*, 1922, 55, 1232.

Tolane unites with two or four atoms of halogen and also with nitrogen peroxide. It melts at 60°.

Certain alcoholic and ketonic derivatives of dibenzyl are of interest. When benzaldehyde is warmed in alcoholic solution with potassium cyanide it yields benzoin, a keto-alcohol of dibenzyl. The mechanism of the condensation is not yet understood.[1]

$$2C_6H_5CHO = \underset{\text{Benzoin}}{C_6H_5 \cdot CO \cdot CHOH \cdot C_6H_5}$$

This reaction is a general one, and may be carried out with other aldehydes of the same type as benzaldehyde.

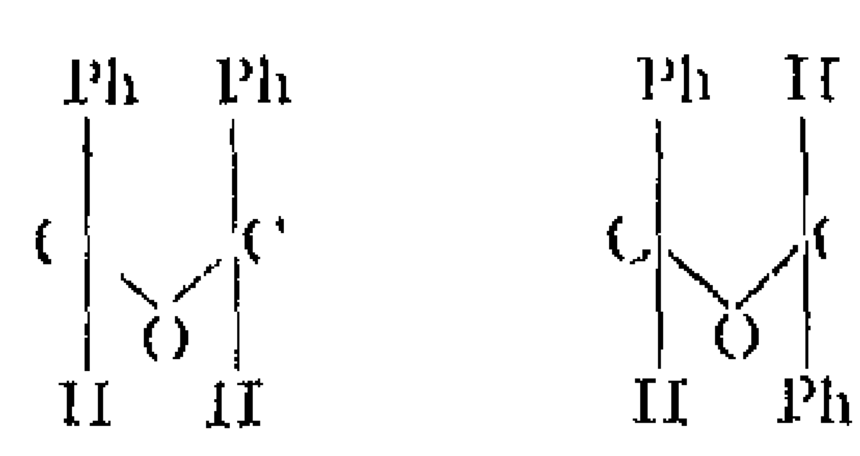
Benzoin crystallises in colourless, odourless prisms, m.p. 137°. It reacts both as a ketone and as a secondary alcohol. Thus it yields an oxime and an osazone, and also ethers and esters. On reduction with sodium amalgam hydrobenzoin is formed.

$$C_6H_5 \cdot \overset{O}{C}—\overset{OH}{CH} \cdot C_6H_5 + 2H = \underset{\text{Hydrobenzoin}}{C_6H_5 \cdot \overset{OH}{CH}—\overset{OH}{CH} \cdot C_6H_5}$$

Benzoin contains an asymmetric carbon atom and has been synthesised in *d*- and *l*-forms by McKenzie and Wren.[2]

Hydrobenzoin, *s-diphenyl-glycol,* is prepared as described above, or by the direct reduction of benzaldehyde by chemical or electrolytic methods. It is also obtained from stilbene dibromide, $C_6H_5 \cdot CHBr \cdot CHBr \cdot C_6H_5$, by treatment with potassium acetate or silver acetate and hydrolysis of the resulting diacetyl ester. It contains two similar asymmetric carbon atoms and thus exhibits the same type of isomerism as tartaric acid. The reactions already quoted actually yield a variable mixture of the two inactive forms, *hydrobenzoin*, m.p. 134°, and *isohydrobenzoin*, m.p. 119°. The latter represents the racemic type[3] and can be resolved into its two optically active components.

Stereoisomeric *diphenylethylene oxides* have been prepared from hydrobenzoin by Read.[4] The symmetrical compound I is inactive, but the dissymmetric oxide II exists in a racemic form and in two optical isomers of high activity.

I  II

[1] A possible explanation of the specific action of the cyanide in effecting this condensation has been suggested by A. Lapworth, *J. C. S.*, 1903, 83, 995. [2] *J. C. S.*, 1908, 93, 309; 1909, 95, 583; 1913, 103, 112. [3] Erlenmeyer, jun., *Ber.*, 1897, 30, 1530. [4] J. Read (*Nature*, 1930, 17).

If benzoin is reduced with zinc and alcoholic hydrochloric or acetic acid, instead of with sodium amalgam, the alcoholic group alone is attacked and desoxybenzoin formed

$$C_6H_5\,\overset{O}{C}-\overset{OH}{CH}\,C_6H_5 + 2H = \underset{\text{Desoxybenzoin}}{C_6H_5\,\overset{O}{C}-CH_2\,C_6H_5} + H_2O$$

Desoxybenzoin, *benzyl-phenyl-ketone*, is generally prepared by the above method It is also formed by the usual methods for preparing ketones, *e g*, by distilling a mixture of calcium benzoate and calcium phenyl-acetate, or from phenyl-acetyl chloride, $C_6H_5\ CH_2\ COCl$, and benzene in the presence of aluminium chloride It crystallises in colourless plates, m p 60° and b p 314°, and on energetic reduction yields dibenzyl Desoxybenzoin resembles aceto-acetic ester in that one hydrogen atom of the methylene group is replaceable by sodium and alkyl groups

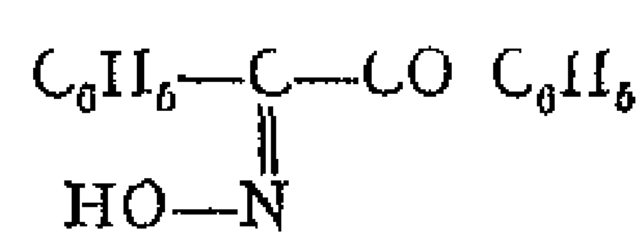
$$C_6H_5\ CO\ CHNa\ C_6H_5 + ICH_3 = \underset{\text{Methyl desoxybenzene}}{C_6H_5\ CO\ \overset{CH_3}{CH}\ C_6H_5} + NaI$$

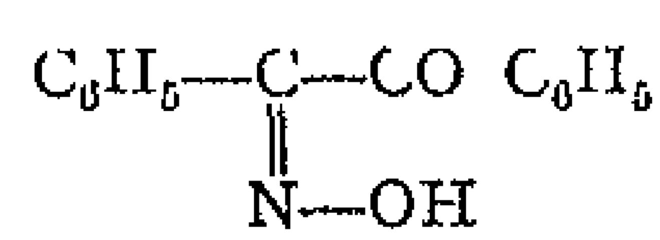
The presence of a secondary alcoholic grouping in benzoin is also shown by the behaviour of the compound on oxidation with nitric acid, when $=CHOH$ is converted into $=CO$ with the production of dibenzoyl or benzil

$$C_6H_5\ CO\ CHOH\ C_6H_5 + O = \underset{\text{Benzil}}{C_6H_5\ CO\ CO\ C_6H_5} + H_2O$$

Benzil, *dibenzoyl*, *diphenyl-glyoxal*, forms yellow prisms, m p 95° Owing to the ease with which it is prepared, it is one of the most accessible of the α-diketones Among its derivatives the oximes are of special interest, since the study of these compounds has contributed largely to our knowledge of the stereochemistry of the nitrogen atom [1]

Two monoximes and three dioximes of benzil are known An examination of the chemical behaviour of the monoximes has led to them being assigned the following space formulæ [2]

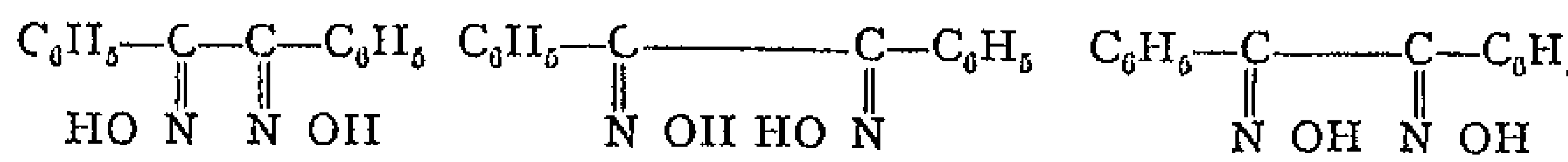

α-Benzil monoxime
m p 140°


β Benzil monoxime
m p 113°

[1] V Meyer and Auwers, *Ber*, 1888, **21**, 790, 815 Hantzsch and Werner, *Ber*, 1890, **23**, 11 Beckmann and Koster, *Ann*, 1893, **274**, 15 [2] These are the newer arrangements as proposed by Meisenheimer For preparation see T W J Taylor and M S Marks, *J C S*, **1930**, 2302

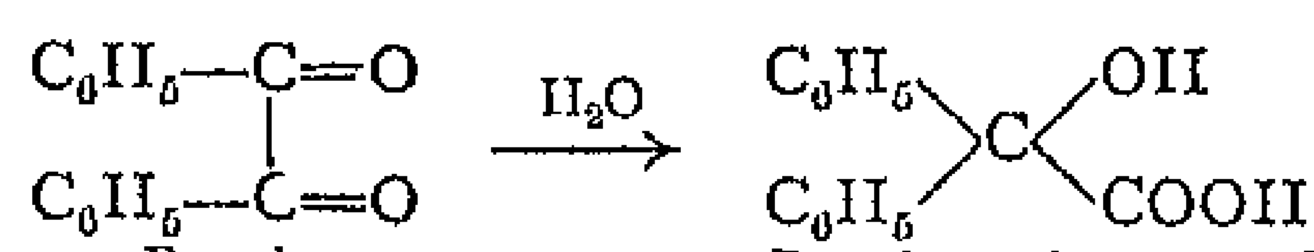
For methods of determining the configuration of the stereoisomeric ketoximes, see p 58

The configurations of the three isomeric benzil-dioximes are now written as follows, involving a transposition of the formulæ previously ascribed to the α- and β forms [1]



α or *anti* form m p 243 244° — β or *syn* form m p 206 — γ or *amphi* form m p 164 165°

A peculiar property of benzil is the change it undergoes when heated with alcoholic potash, when an intramolecular rearrangement takes place with the formation of *benzilic acid*



Benzil — Benzilic acid, m p 150° (Diphenyl glycollic acid)

This reaction resembles the conversion of phenanthraquinone into diphenylene-glycollic acid (p 492), and of β-naphthaquinones into oxindene-carboxylic acids

s **Tetraphenyl ethane**, $(C_6H_5)_2CH \cdot CH(C_6H_5)_2$, is obtained in various ways, *e g* by the interaction of chloral and benzene in the presence of aluminium chloride It forms colourless crystals, m p 207 5° and b p 379 to 383°

Unsymmetrical tetraphenyl ethane, $(C_6H_5)_3C \cdot CH_2 \cdot C_6H_5$, has been prepared by the action of benzyl magnesium chloride on triphenyl chloromethane [2]

$$(C_6H_5)_3C \cdot Cl + C_6H_5 \cdot CH_2 \cdot MgCl = (C_6H_5)_3C \cdot CH_2 \cdot C_6H_5 + MgCl_2$$

It crystallises in monoclinic crystals, m p 144°

Tetraphenyl ethylene, $(C_6H_5)_2C : C(C_6H_5)_2$, m p 221°, can be obtained by the action of zinc dust on benzophenone chloride

Pentaphenyl ethane, $(C_6H_5)_3C \cdot CH(C_6H_5)_2$, results when a mixture of diphenyl bromo methane and triphenyl chloro methane, in ethereal solution, is treated with magnesium [2] It melts about 175° to 180°

$$(C_6H_5)_3C \cdot Cl + Mg + Br \cdot HC(C_6H_5)_2 = (C_6H_5)_3C \cdot CH(C_6H_5)_2 + MgClBr$$

Hydrocarbons containing phenyl groups linked to unsaturated

[1] J Meisenheimer, *Ann*, 1920, 400, 130 In accordance with a proposal of Hantzsch the terms *syn*, *anti* and *amphi* are employed in the sense indicated in the above formulæ in describing the stereoisomeric dioximes (See also general notes in the chapter on "Stereo chemistry") [2] Gomberg and Cone, *Ber*, 1906, 39, 1461

carbon have the property of uniting directly with alkali metals,[1] as in the following examples ($C_6H_5 = Ph$)

$$Ph_2C\ CPh_2 \xrightarrow{2Na} Ph_2C(Na)\ C(Na)Ph_2$$
$$2Ph_2C\ CH_2 \xrightarrow{2Na} Ph_2C(Na)\ CH_2\ CH_2\ C(Na)Ph_2$$

A similar addition is observed with certain hydrocarbons in which unsaturated carbon is linked to other unsaturated groups

VI —HIGHER HOMOLOGUES OF DIPHENYL-ETHANE AND THEIR DERIVATIVES

Whereas the compounds already described in this chapter contain aromatic residues linked together by one or two "methane" carbon atoms, a number of substances are also known in which a longer aliphatic chain is present between the aromatic groups

Dibenzyl-methane, *αγ diphenyl-propane,* $C_6H_5\ (CH_2)_3\ C_6H_5$, b p 299°, is formed by reducing dibenzyl-ketone, $C_6H_5\ CH_2\ CO\ CH_2\ C_6H_5$ (m p 40°, b p 330°), by means of hydriodic acid The ketone is obtained by the dry distillation of calcium phenyl-acetate[2] We may also consider as derivatives of dibenzyl-methane certain of the polyketones discussed in previous chapters, which are of interest in connection with the theory of tautomerism Among these are *dibenzoyl-methane,* $(C_6H_5CO)_2CH_2$, *dibenzoyl-acetyl-methane,* $(C_6H_5CO)_2CH(COCH_3)$, and *tribenzoyl-methane,* $(C_6H_5CO)_3CH$

αγ-**Tetraphenyl propane,** $(C_6H_5)_2CH\ CH_2\ CH(C_6H_5)_2$, m p 139°, is formed by the reduction of tetraphenyl-allene with phosphorus and hydrogen iodide, or with sodium and alcohol **Tetraphenyl allene**[3] is produced when the barium salt of diphenyl-acetic acid is distilled, tetraphenyl-acetone being obtained as an intermediate product

$$(C_6H_5)_2CH\ CO\ O\ Ba\ O\ OC\ CH(C_6H_5)_2 \xrightarrow{-BaCO_3}$$
$$\underset{\text{Tetraphenyl acetone}}{(C_6H_5)_2CH\ CO\ CH\ (C_6H_5)_2} \xrightarrow{-H_2O} \underset{\text{Tetraphenyl allene}}{(C_6H_5)_2C\ C\ C(C_6H_5)_2}$$

A more convenient method of preparation is from benzal-acetophenone[3] It forms colourless crystals of melting-point 164° to 165°

Dibenzyl-ethane, *αδ-diphenyl-butane,* $C_6H_5\ CH_2\ CH_2\ CH_2\ CH_2\ C_6H_5$, m p 52°, has been obtained by the reduction of diphenyl butylene, $C_6H_5\ CH\ CH\ CH_2\ CH_2\ C_6H_5$

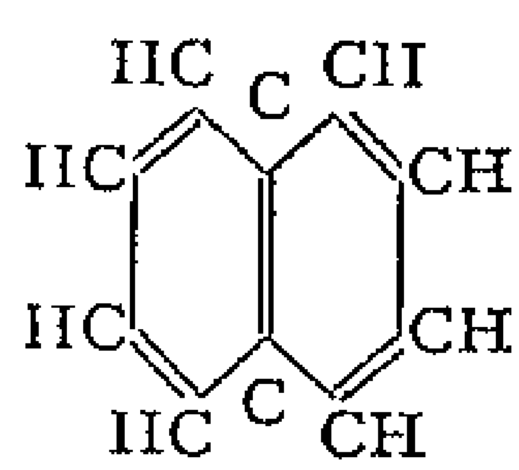
Diphenyl-diacetylene, $C_6H_5\ C{\equiv}C{-}C{\equiv}C\ C_6H_5$, the parent hydrocarbon of indigo blue, is obtained by the oxidation of cuprous phenyl-acetylide, $(C_6H_5\ C\ C)_2Cu$ As will be seen later, its ortho dinitro-derivative may be converted into indigo

[1] W Schlenk and E Bergmann, *Ann*, 1928, 468, 1, 98 [2] H Apitzsch, *Ber*, 1904, 37, 1428 [3] Vorländer and Siebert, *Ber*, 1906, 39, 1024

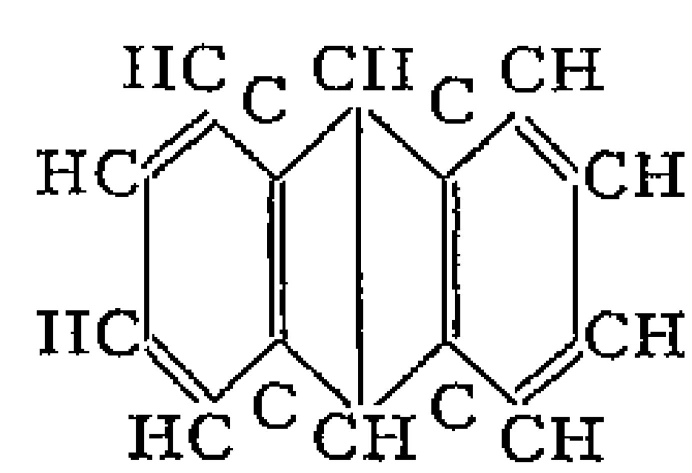
XIV

Condensed Polynuclear Compounds

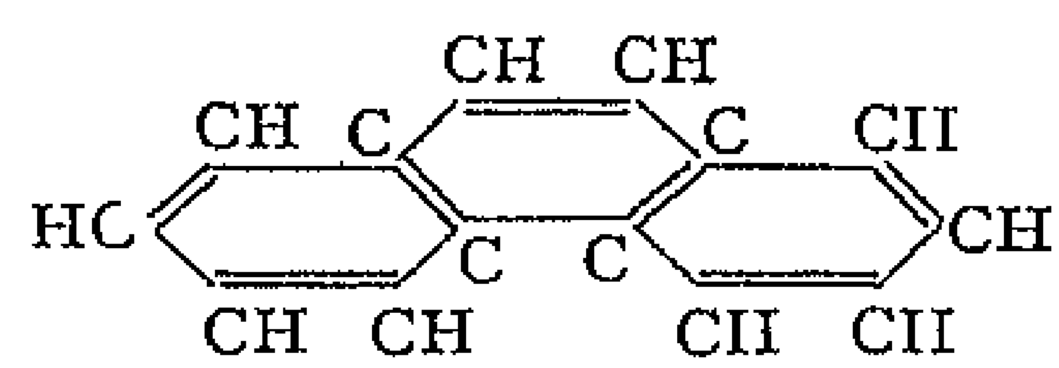
Under this heading are described compounds containing several benzene nuclei linked together in such a manner that each pair possesses two carbon atoms in common, as in the following formulæ



Naphthalene



Anthracene



Phenanthrene

These hydrocarbons, like benzene, are found in coal tar, and as might be expected are on the whole aromatic in character

An example of a compound formed by the combination of benzene nuclei with a five-membered carbon ring has previously been met with in *fluorene* Owing to its genetic relationship to diphenylmethane, however, this substance is more conveniently treated in the foregoing chapter Another compound consisting of a benzene nucleus condensed with a five-membered ring is *indene* This is only of secondary interest and is treated briefly in connection with naphthalene

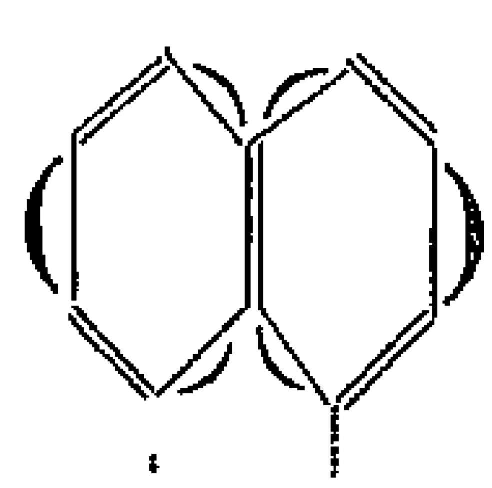
Naphthalene Group

Naphthalene, $C_{10}H_8$, is obtained from the fraction of coal tar known as "middle or carbolic oil," boiling between 170° and 240° (see p 368) The crystals which deposit from the oil on cooling are separated under pressure from liquid impurities, and further purified by heating with a small amount of sulphuric acid and subsequent sublimation Naphthalene forms shining white rhombic leaflets of an unpleasant, penetrating smell and burning taste It melts at 79°, boils at 218° and very readily sublimes It is insoluble in water, dissolves with difficulty in cold alcohol, but readily in hot alcohol or in ether With picric acid it forms a double compound $C_{10}H_8$, $C_6H_2(NO_2)_3OH$,

m.p. 149°, by means of which it can be quantitatively estimated.[1] The occurrence of naphthalene in coal tar is probably due to the ease with which it is formed when organic substances are heated to a high temperature in absence of air. It is a compound of great industrial value, serving as it does for the preparation of naphthols, naphthylamines, etc., for dye-stuffs, and also of the phthalic acid required in the synthesis of indigo. Its use as a preventative against moths is well known.

Constitution and Synthesis of Naphthalene

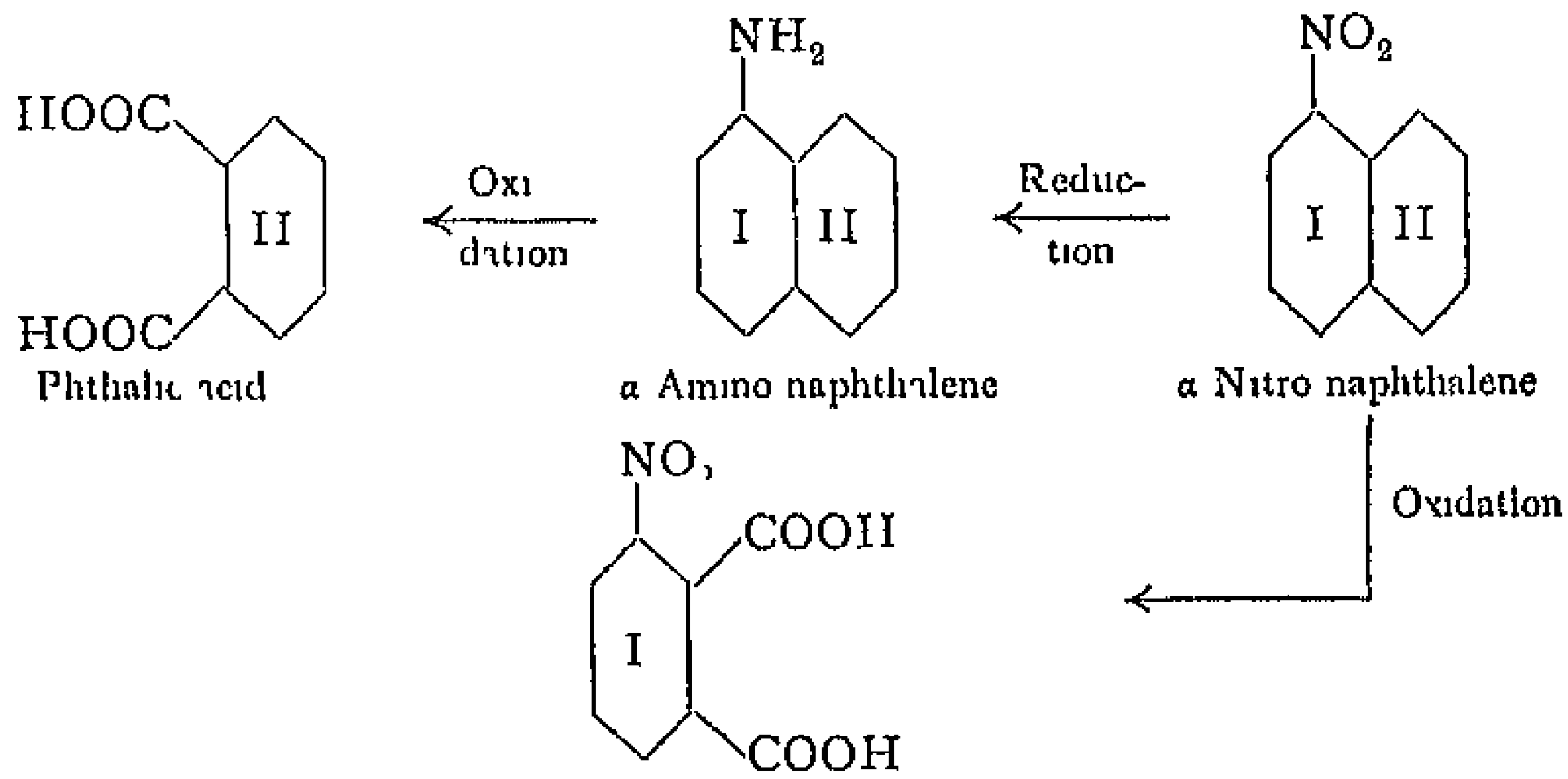
The symmetrical formula for naphthalene given on p. 517, according to which two benzene rings are joined together with two carbon atoms in common,[2] was first put forward by Erlenmeyer in 1866. Although insufficient to meet all the facts of the case, this formula satisfactorily explains the isomerism observed among naphthalene derivatives, and if modified in accordance with Thiele's theory of partial valencies[3] also gives a good representation of the chemical behaviour of naphthalene. It will be remembered that a somewhat similar difficulty exists in connection with the Kekulé formula for benzene. Proof of the presence of two benzene rings, having two adjacent carbon atoms in common, is furnished by the *behaviour of naphthalene and its substitution products on oxidation*.[4] When naphthalene itself is oxidised it yields phthalic acid (see p. 443). Consequently the formula $C_{10}H_8$ of naphthalene may, as a first step, be expanded to $C_6H_4=C_4H_4$. Now α-nitro-naphthalene, which is obtained from naphthalene on treatment with nitric acid and which may be supposed[5] to have the nitro-group attached to benzene ring I (p. 519), yields on oxidation nitro-phthalic acid. Hence in this case the benzene nucleus I remains intact and the group C_4H_4 is again oxidised away to two carboxyl groups, leading to formula *a* for naphthalene. If, however, nitro-naphthalene is reduced to the amino-compound and subsequently oxidised, phthalic acid and not amino-phthalic acid is obtained. Here ring I has been destroyed and II remains unchanged, thus giving formula *b* for naphthalene.



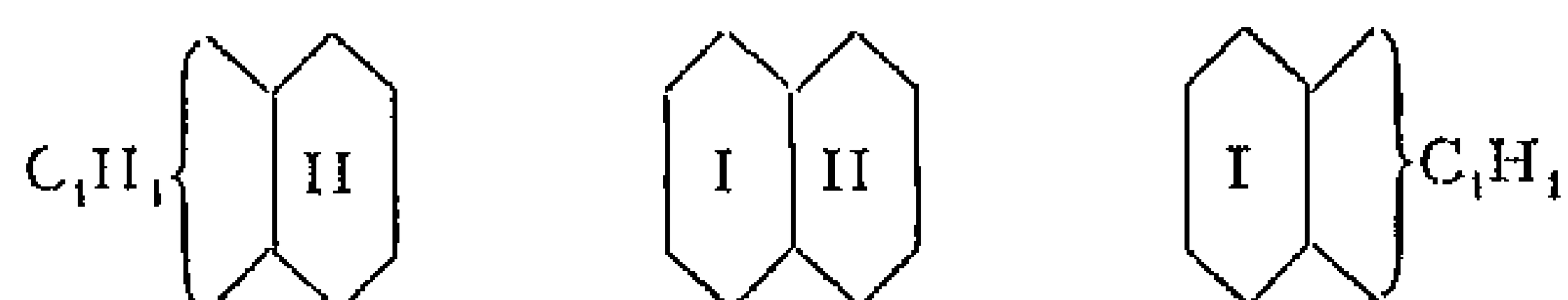
On comparing the formulæ *a* and *b*, it is seen at once that the group C_4H_4 must be united to two adjacent carbon atoms of the ring

[1] W. P. Jorissen and J. Rutten, *Chem. Weekblad*, 1909, 6, 261. [2] Unsymmetrical formulæ for naphthalene have lately been advocated by Auwers and Frühling (*Ann.*, 1921, 422, 211) and by Mayer and Bansa (*Ber.*, 1921, 54, 19). *Cf.* also Weinberg, *Ber.*, 1921, 54, 2168. [3] J. Thiele, *Ann.*, 1899, 306, 136. [4] Graebe, *Ann.*, 1866, 149, 20. [5] It will readily be seen that the argument is not affected by this assumption. The nitro group could equally well be supposed to be contained in the nucleus II.

I or II to form a new benzene ring, *i e*, that naphthalene must consist of two symmetrically joined benzene nuclei



Phthalic acid — a Amino naphthalene — a Nitro naphthalene — Nitro phthalic acid



Formula *b* — Naphthalene — Formula *a*

This structure is also confirmed by a number of *syntheses of naphthalene and its derivatives*, among which the following may be mentioned

1 Naphthalene is formed when phenyl-butylene or its dibromide is led in the vapourous state over red-hot lime

$$C_6H_5\left\langle\begin{array}{l}CH_2-CH_2\\ \quad\ |\\ CH_2=CH\end{array}\right. \longrightarrow C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\ |\\ CH=CH\end{array}\right. + 2H_2$$

Phenyl butylene — Naphthalene

2 Baeyer and Perkin obtained naphthalene and derivatives of tetrahydro-naphthalene by bringing *o* xylylene dibromide into reaction with the disodium compound of ethane tetracarboxylic ester

$$C_6H_4\left\langle\begin{array}{l}CH_2Br\\ CH_2Br\end{array}\right. + \begin{array}{l}NaC(CO_2C_2H_5)_2\\ \quad |\\ NaC(CO_2C_2H_5)_2\end{array} \longrightarrow C_6H_4\left\langle\begin{array}{l}CH_2-C(CO_2C_2H_5)_2\\ \qquad\ \ |\\ CH_2-C(CO_2C_2H_5)_2\end{array}\right.$$

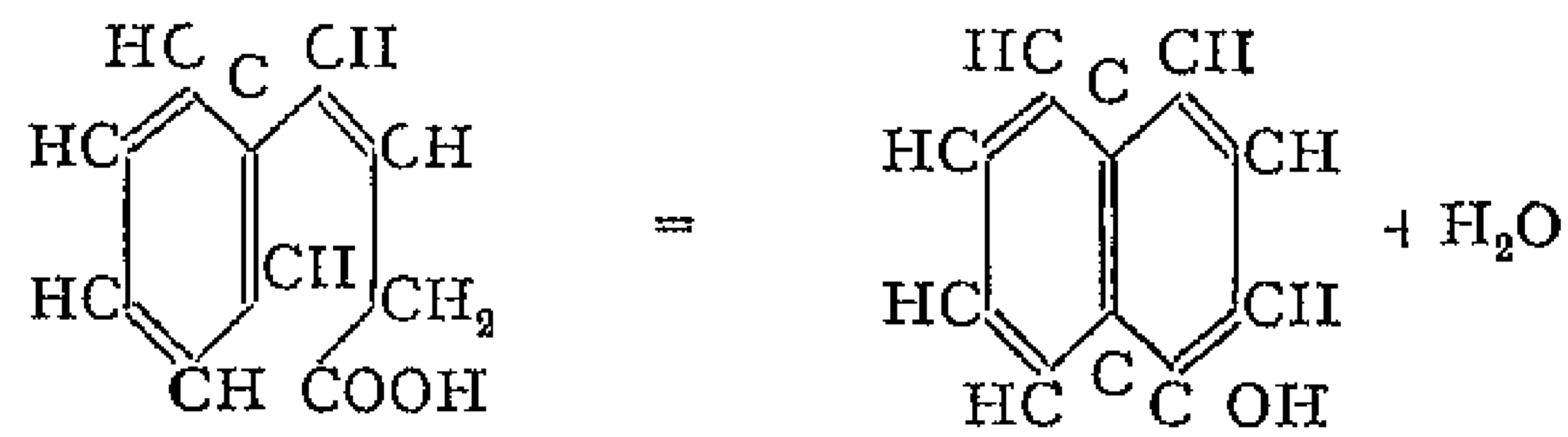
Ethyl tetrahydronaphthalene tetracarboxylate

When the ester so obtained is boiled with alkali it is hydrolysed with the simultaneous removal of carbon dioxide, to give tetrahydronaphthalene dicarboxylic acid, from which, by distillation of the silver salt, naphthalene itself was prepared

$$C_6H_4\left\langle\begin{array}{l}CH_2\ CH\ CO_2H\\ \qquad\ |\\ CH_2\ CH\ CO_2H\end{array}\right. \xrightarrow[-4H]{-2CO_2} C_6H_4\left\langle\begin{array}{l}CH=CH\\ \quad\ |\\ CH=CH\end{array}\right.$$

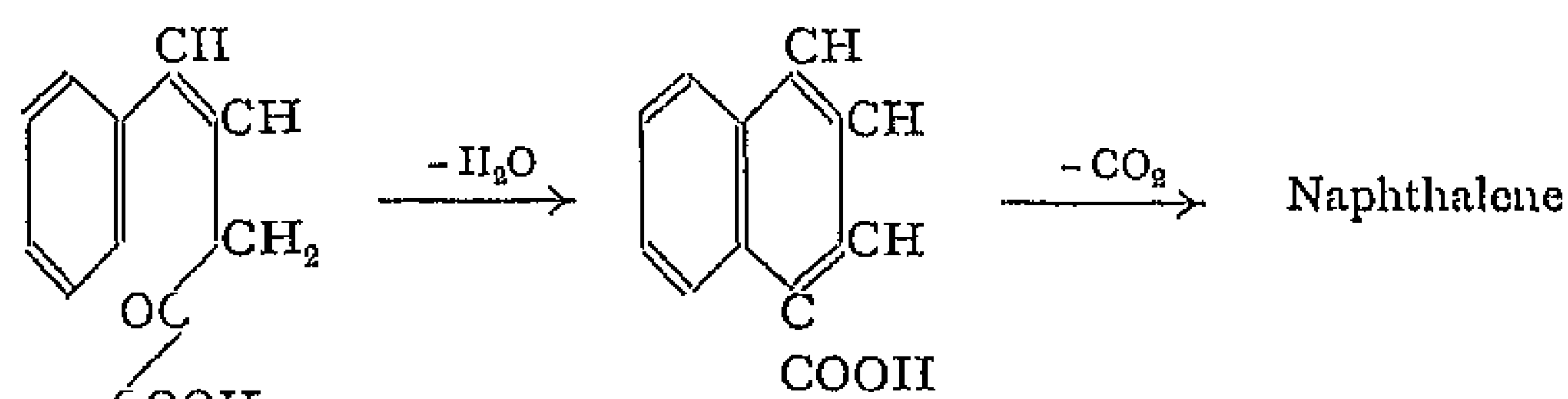
Tetrahydronaphthalene dicarboxylic acid — Naphthalene

3 Phenyl-isocrotonic acid, on being heated, is converted into α-naphthol, a monohydroxy derivative of naphthalene [1]



Phenyl-isocrotonic acid α-Naphthol

4 When cinnamylidene-hippuric acid, or the cinnamyl-pyruvic acid obtained from it on decomposition, is heated with concentrated hydrochloric acid at 110° to 120°, α-naphthoic acid, and finally naphthalene, is produced [2]



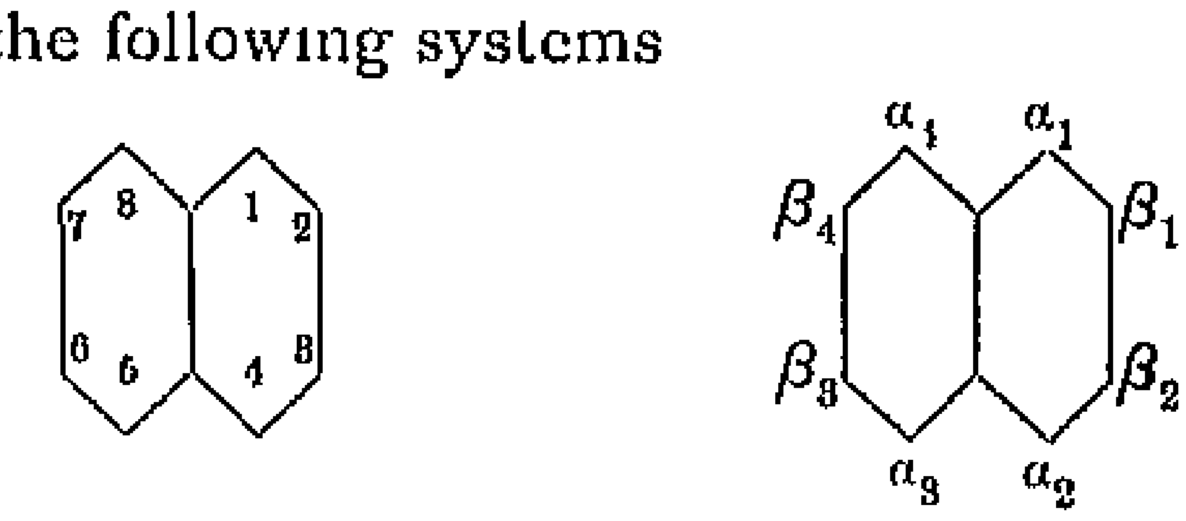
Cinnamyl pyruvic acid α-Naphthoic acid

5 *o* Xylylene cyanide condenses with compounds such as *o*-diketones, ketonic esters and oxalic esters, in the presence of sodium ethoxide, to yield naphthalene derivatives [3]

$$C_6H_4\left\langle\begin{matrix} CH_2\ CN \\ CH_2\ CN \end{matrix}\right. + \begin{matrix} CO\ R \\ | \\ CO\ R_1 \end{matrix} = C_6H_4\left\langle\begin{matrix} C(CN) \\ C(CN) \end{matrix}\right. \begin{matrix} C\ R \\ | \\ C\ R_1 \end{matrix} + 2H_2O$$

Isomerism of Naphthalene Derivatives

From the formula for naphthalene it is possible to predict the existence of a number of isomeric substitution products In order to indicate the position of substituent atoms or radicals, use is made of one or other of the following systems



It will be seen that even the mono-derivatives of naphthalene can exist in two series, according to whether or not the substituent is attached to an atom adjacent to one of the two carbon atoms common

[1] Fittig and Erdmann, *Ber.*, 1883, 16, 43 *Ann.*, 275, 284 [2] E Erlenmeyer and Kunlin, *Ber.*, 1902, 35, 384 [3] O Hinsberg, *Ber.*, 1910, 43, 1360

to both rings Those compounds formed by the replacement of one of the four equivalent hydrogen atoms 1, 4, 5, or 8 are known as α-compounds, and those obtained by substituting one of the four equivalent atoms 2, 3, 6, or 7 as β-compounds Whether a radical is attached in the α- or β-position can frequently be determined by oxidising the substance under consideration to the corresponding phthalic acid derivative (*cf* p 519)

A disubstitution product of naphthalene may occur in 10 isomerides if the two substituents are similar, or in 14 isomerides if they are different With the entry of more than two atoms or groups into the molecule the number of isomerides is very much larger

Compounds in which two substituents are attached to two adjacent carbon atoms correspond in their behaviour to the ortho-derivatives of the benzene series Similar behaviour with respect to anhydride formation and condensation is also shown by 1 8- or 4 5-derivatives, these positions being known as *peri*-positions **Peri-derivatives** possess in an enhanced degree the properties characteristic of *o*-compounds This may be seen from a comparison of *peri*-amino-naphthoic acid with anthranilic acid, of naphthalic with phthalic acid, and of 1 8-naphthylene-diamine with *o*-phenylene-diamine In all cases where *o*-diamines are able to take up a new element to form a five-membered ring-system, the *peri*-diamines can similarly form a six-membered ring In the latter case, however, the reaction occurs much more readily than with the *o*-derivatives[1]

Chemical Behaviour of Naphthalene

As already stated, naphthalene shows in general the properties characteristic of aromatic hydrocarbons It reacts with halogens, nitric acid and sulphuric acid in a similar manner to benzene, with the formation of chloro-, nitro- and sulphonic derivatives In many ways, however, it differs from benzene

The chief distinction between benzene and naphthalene is the ease with which the latter forms additive compounds, the addition beginning at the α-positions (compare formula on p 518)

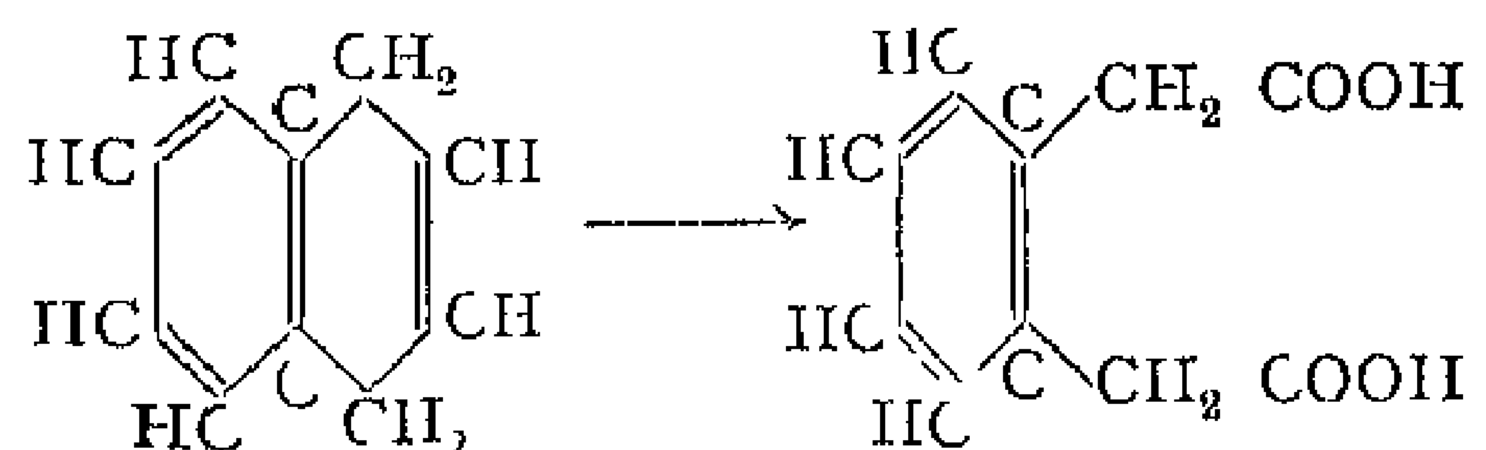
In this respect naphthalene is less saturated than benzene On reduction, for example, it first yields $\alpha_1\alpha_2$-dihydro-naphthalene, and on oxidation it readily gives α-naphthaquinone (see index) Halogen is very easily added on, and as in the case of direct substitution, again leads to the exclusive formation of α-derivatives Exceptional behaviour is shown on sulphonation, which yields a mixture of α- and β-sulphonic acids

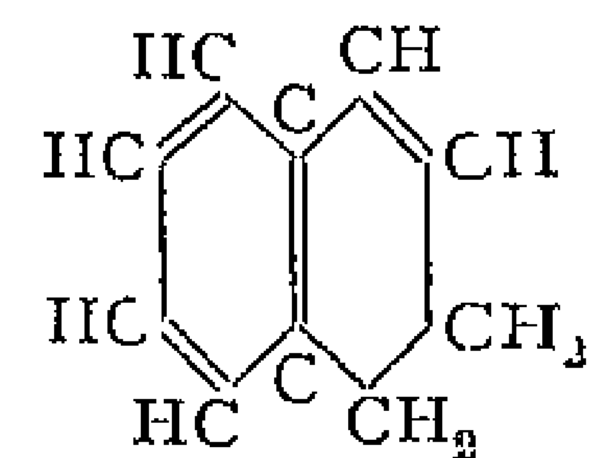
$\alpha_1\alpha_2$-Dihydro-naphthalene, Δ^2-dihydro-naphthalene, $C_{10}H_{10}$, is obtained when naphthalene is reduced with sodium in boiling alcoholic solution It melts at 15° and boils at 212° On oxidation the compound

[1] Bamberger, *Ber*, 1887, 20, 241 Sachs, *Ann*, 1909, 365, 53

is converted into *o*-phenylene-diacetic acid, proving that the hydrogen atoms have assumed the 1 4-position, in accordance with Thiele's theory

I II



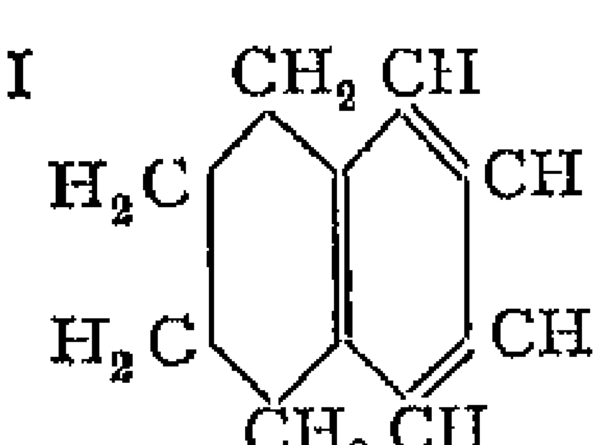


Δ^2 Dihydro naphthalene — *o* Phenylene diacetic acid — Δ^1-Dihydro naphthalene

Dihydro-naphthalene resembles ethylene in its unsaturated properties, two monovalent atoms or groups (H_2, Br_2, HOCl, etc) being readily added on to the β_1 β_2 positions On the other hand, dihydro- and tetrahydro-naphthalene both possess the tendency characteristic of partially hydrogenated aromatic systems to pass into true aromatic types, as shown by their decomposition merely on heating to give naphthalene and hydrogen If symmetrical Δ^2-dihydro-naphthalene is heated to 140° with 5 per cent sodium ethylate solution,[1] the position of the double bond is shifted with the formation of **Δ^1-dihydro-naphthalene** (II), m p $-7°$ The constitution of this compound is shown by the production of hydrocinnamic-*o*-carboxylic acid on oxidation with permanganate, in the same manner as Δ^2-dihydro-naphthalene gives *o*-phenylene-diacetic acid

1 2 3 4-Tetrahydro naphthalene, tetralin (III), has recently become readily accessible[2] and is prepared industrially on a large scale In the technical preparation, naphthalene is first fused with finely-divided metals of low melting-point in order to remove sulphur and other compounds, which would "poison" the catalyst used in subsequent operations The purified naphthalene is then placed in an autoclave provided with stirring apparatus and treated with hydrogen under pressure, in the presence of a nickel salt. The reaction slows down after four atoms of hydrogen have been taken up As the change is an exothermic one, heat need only be supplied to start the reaction

III



Tetrahydro naphthalene, tetralin

The tetralin of commerce is a colourless liquid, b p 206° to 208°, D^{20} 0 974 to 0 976, m p $-30°$ to $-27°$, and flash-point 78° At the ordinary temperature the substance is stable, but the hot vapour is oxidised in air Tetralin is a good solvent for sulphur, fats, resins and many other organic products, and hence is employed industrially as a solvent in the preparation of varnishes and lacquers, and admixed with benzene and

[1] F Straus and Lemmel, *Ber*, 1913, 46, 232 For dihydro naphthalene, see also Willstätter and King, *Ber*, 1913, 46, 527 [2] G Schroeter, *Ann*, 1922, 426, 1, 17, 83 *Ber*, 1924, 57, 1990

alcohol as a fuel for internal combustion engines. Pure tetralin is obtained from the sulphonic acid by the action of superheated steam (b.p. 206.5° at 755 corr.).

When tetralin is treated with bromine[1] it behaves in the same manner as an alkyl benzene. In the cold, no reaction takes place in the absence of light, but on the addition of a little iron or a trace of iodine, substitution readily occurs in the benzene nucleus, even at −10°, with the formation of a mixture of *ar*-*α*- and *ar*-*β*-bromo-tetrahydro-naphthalenes,[2] b.p. 140° to 145° under 15 mm. Under the influence of light, or at a higher temperature in the absence of catalysts, halogen attacks the reduced ring.

Substitution in the aromatic half of tetralin does not follow the same laws as in the case of naphthalene.[3] Reactions such as nitration, bromination and chlorination yield a mixture of *ar*-*α*- and *ar*-*β*-substitution products, which can often be satisfactorily separated by distillation and freezing out, whereas naphthalene gives almost exclusively *α*-compounds, and the corresponding *β*-derivatives can only be obtained by more or less troublesome indirect methods. Other reactions, such as the entrance of carboxyl, alkyl and acyl groups into tetralin under the influence of aluminium chloride, proceed almost completely in the direction of the *β*-compounds, whilst with naphthalene, on the other hand, the same conditions frequently furnish a difficultly separable mixture of *α*- and *β*-products. Since tetralin and its substitution products readily give up hydrogen to form the corresponding naphthalene compounds, we have here an indirect method of preparing from tetralin those derivatives of naphthalene which can only be obtained with much labour by direct means.

Decahydro naphthalene, decalin, $C_{10}H_{18}$, is prepared from tetralin by further hydrogenation with fresh catalyst under 12 to 15 atmospheres pressure. It boils at 189° to 191°. D_{1}^{15} 0.8842. According to Hückel[4] decalin exists in a *cis*-form (b.p. 193°, D_{4}^{20} 0.898, n_{D}^{20} 1.48279) and a *trans*-modification (b.p. 185°, D_{1}^{20} 0.872, n_{D}^{20} 1.47009).

Naphthalene dichloride, $C_{10}H_8Cl_2$, is produced as a yellow oil when naphthalene is treated with potassium chlorate and hydrochloric acid. At about 50° it begins to decompose into hydrochloric acid and *α*-chloro-naphthalene. **Naphthalene tetrachloride,** $C_{10}H_8Cl_4$, m.p. 182°, is formed by leading chlorine into a solution of naphthalene in chloroform. On boiling with alcoholic potash it is converted into dichloro-naphthalene. As would be expected, all four chlorine atoms are contained in the same benzene ring, since when oxidised with nitric acid the compound yields phthalic acid.

With ozone naphthalene forms an explosive crystalline **diozonide** in which two molecules of ozone are attached to one of the benzene nuclei.

[1] J. v. Braun and Kirschbaum, *Ber.*, 1921, 54, 597. The prefix *ar* refers to the unreduced or aromatic half of the molecule. [2] J. v. Braun, Hahn und Seemann, *Ber.*, 1922, 55, 1687. [4] *C.*, 1923, III, 766. R. Willstätter and F. Seitz, *Ber.*, 1924, 57, 683.

SUBSTITUTION PRODUCTS OF NAPHTHALENE[1]

(a) *Homologues*

α-Methyl-naphthalene, $C_{10}H_7 \cdot CH_3$, m.p. −20°, b.p. 240° to 243°, and *β-methyl-naphthalene*, m.p. 32.5°, b.p. 241° to 242°, are found with dimethyl-naphthalenes in coal tar, petroleum and guaiacum resin.[2] Synthetically, they may be prepared by methods similar to those employed for the benzene homologues, such as by treating the bromo-naphthalenes with alkyl halides and sodium, and by the Friedel-Crafts reaction from alkyl iodides or bromides and naphthalene in the presence of aluminium chloride.

(b) *Halogen and Nitro-derivatives*

As already mentioned, the action of chlorine or bromine on the hydrocarbon yields α-substitution products. The β halogen compounds are best prepared from the hydroxy-, amino- or sulphonic derivatives by replacing the substituent with halogen according to methods described under benzene. The halogen atoms in these derivatives are less difficult to remove than those in the corresponding benzene compounds, but are nevertheless far more firmly attached than in the alkyl halides, and cannot be exchanged by boiling with alkalis.

α-Chloro-naphthalene, $C_{10}H_7Cl$, boils at 263°. It is formed by the chlorination of boiling naphthalene, but is best prepared from α-amino-naphthalene by way of the diazo compound. **β-Chloro-naphthalene** melts at 61° and boils at 265°. **Dichloro-naphthalene**, $C_{10}H_6Cl_2$, is known in all of the ten possible isomeric forms.

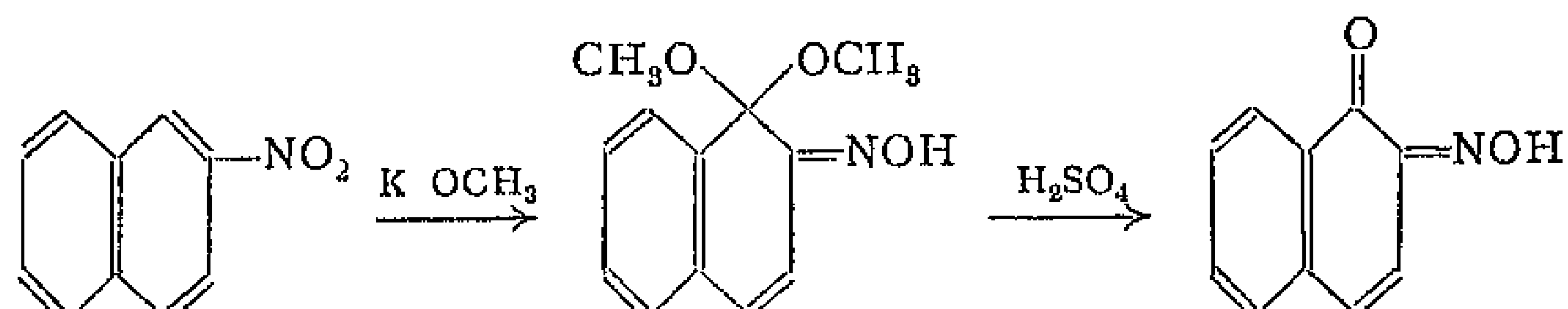
The nitration of naphthalene with concentrated nitric acid at ordinary temperature leads mainly to the formation of **α-nitro-naphthalene**, free from the isomeric β-compound. It crystallises in yellow needles, m.p. 61°, b.p. 304°. By way of the amino- and diazo-derivatives it may be converted into the hydroxy compound, α-naphthol, identical with the product obtained synthetically from phenyl-isocrotonic acid (see p. 520). Hence the nitro-group must have occupied the α-position. Since the nitro-group can be exchanged by the usual methods for a variety of atoms and radicals, α-nitro-naphthalene has frequently been of aid in determining the position of the substituent in mono-derivatives of naphthalene. It is used industrially in the preparation of α-naphthylamine.

Energetic nitration of naphthalene at higher temperature yields di-, tri- and tetra-nitro-naphthalenes, of which the first are of importance in the dye-stuff industry.

β-Nitro-naphthalene is prepared from technical β-naphthylamine by diazotisation in nitric acid solution and treating the naphthalene diazonium nitrate with cuprous oxide,[3] or from β-nitro-tetralin by

[1] For a useful summary of naphthalene derivatives see *Naphthalin Derivate*, by van der Kam (M. Nijhoff, Hague, 1927). [2] See *Ber.*, 1918, 51, 1603; *Ber.*, 1919, 52, 316, 370. [3] For laboratory details, see Meisenheimer and Witte, *Ber.*, 1903, 36, 4153.

dehydrogenation with the aid of bromine[1] It forms yellow crystals, m p 79° Under the influence of methyl alcoholic potash it undergoes a peculiar reaction,[2] similar to that given by 9-nitro-anthracene, and becomes transformed into an alkali-soluble compound which on further treatment with mineral acid yields naphthaquinone-oxime, isomeric with the original nitro-naphthalene[3]



β Nitro naphthalene β Naphthaquinone 2 oxime dimethylacetal β Naphthaquinone 2 oxime (2 nitroso-1 naphthol)

(c) *Naphthalene Sulphonic Acids, Naphthols, Naphthylamines*

When heated with concentrated sulphuric acid, naphthalene gives a mixture of the two isomeric **naphthalene-sulphonic acids**, $C_{10}H_7$ SO_2OH, below 100° more of the α-form is produced and above 160° more of the β-compound The α-acid, on being heated with sulphuric acid, is converted into the β-acid They are deliquescent crystalline substances which when fused with caustic alkali yield the corresponding naphthols

$$C_{10}H_7\ SO_3Na + 2NaOH = C_{10}H_7\ ONa + Na_2SO_3$$

On the large scale one part of sodium naphthalene-sulphonate is melted under pressure at about 300° with a concentrated solution of two parts of sodium hydroxide, in iron vessels provided with stirring apparatus From the sodium naphtholate so formed, naphthol may be precipitated by means of sulphuric acid or carbon dioxide, and purified by distillation alone or with superheated steam

α-**Naphthol**, m p 94° and b p 280°, crystallises in needles For a synthesis see p 520 β-**Naphthol**, m p 122° and b p 286°, forms leaflets In chemical behaviour the naphthols show a general resemblance to the phenols, although the hydroxyl groups are much more mobile than in the latter compounds For example, when heated with ammonia the naphthols are readily converted into the naphthylamines On reduction with sodium and alcohol, naphthols yield *tetrahydro-naphthols*, $C_{10}H_{11}$ OH In the case of α-naphthol the four hydrogen atoms almost exclusively enter the hydroxyl-free ring to form *ar*-**tetrahydro-α-naphthol**,[4] (C_4H_8) C_6H_3 OH, which possesses the character of a true phenol With β-naphthol the four hydrogen atoms not only enter the hydroxyl-free ring to give *ar* **tetrahydro**

[1] J v Braun and co workers, *Ber*, 1922, 55, 1695 [2] Meisenheimer and Witte, *loc cit*, p 4161 [3] Another change occurs simultaneously, though to a much smaller extent, leading to the formation of azoxy- and azo compounds by the reducing action of the methyl alcoholic potash on β nitro naphthalene (*cf* nitrobenzene) [4] For the use of the prefixes *ar* and *ac*-, see p 528

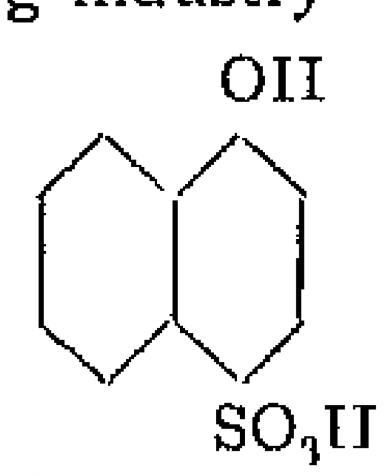
β-naphthol, $(C_4H_8)\,C_6H_3OH$, but also that containing the —OH group to form *ac*-**tetrahydro-β-naphthol**, $(HO\cdot C_4H_7)\,C_6H_4$. The first of these resembles the phenols in properties, and the latter the aliphatic alcohols. These interesting differences are discussed in more detail under the naphthylamines.

A large number of ethers, sulphonic acids and nitro-derivatives of the naphthols have been prepared.[1] The hydroxy-derivatives of the naphthalene series also resemble the phenols in reacting in tautomeric forms.[2]

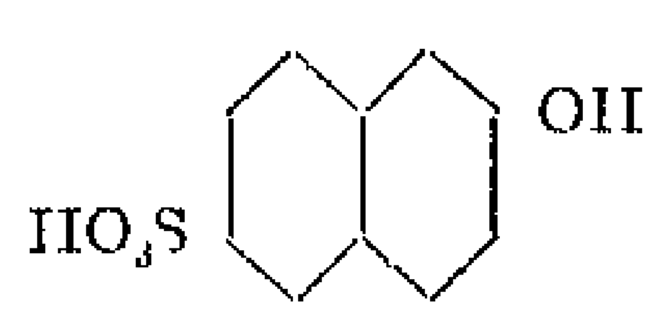
β-Naphthyl methyl ether, $C_{10}H_7\cdot OCH_3$, m.p. 72°, is obtained by heating β-naphthol with methyl alcohol and hydrochloric acid, or by heating sodium β-naphtholate with potassium methyl sulphate. It has a smell like oil of orange flowers (neroli oil), and is used under the name of **nerolin** in the preparation of perfumes.

Dinitro-α-naphthol, $C_{10}H_5(NO_2)_2OH$, $[\overset{1}{OH}:\overset{2}{NO_2}:\overset{4}{NO_2}]$, is prepared by treating α-naphthol-disulphonic acid (1:2:4) with nitric acid, and crystallises in needles, m.p. 138°. It is almost insoluble in water but its salts are comparatively soluble, the sodium or less frequently the potassium compound being placed on the market under the name of **Martius yellow**. In acid bath it dyes wool and silk a golden yellow colour. **Naphthol yellow S** is the potassium salt of the sulphonic derivative of dinitro-α-naphthol. It is a more permanent dye than Martius yellow.

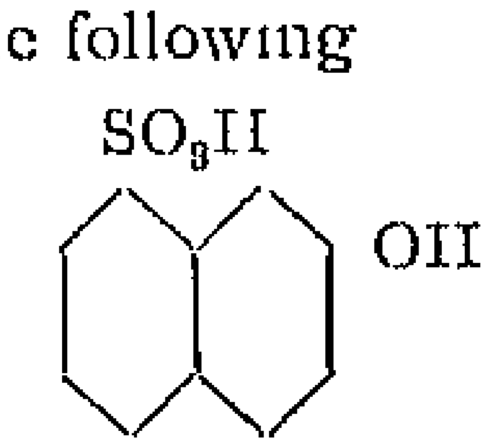
Naphthol-sulphonic acids are produced either by direct sulphonation, by fusing polysulphonic derivatives of naphthalene with alkali hydroxide, or by replacing the NH_2-group in naphthylamine sulphonic acids with the hydroxyl group. They are extensively used in the dyeing industry. Among the more important are the following:



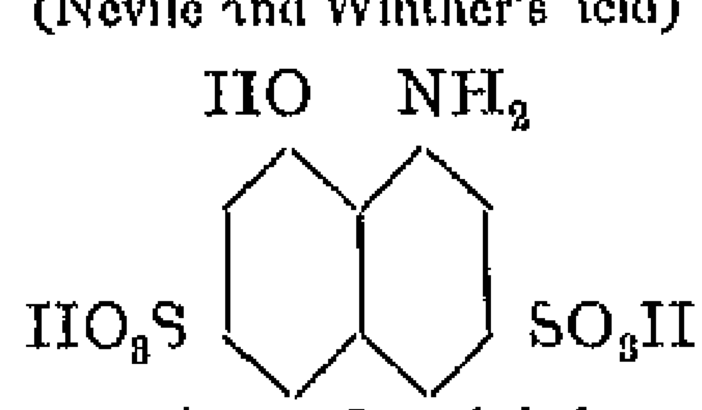
1-Naphthol-4-sulphonic acid (Nevile and Winther's acid)



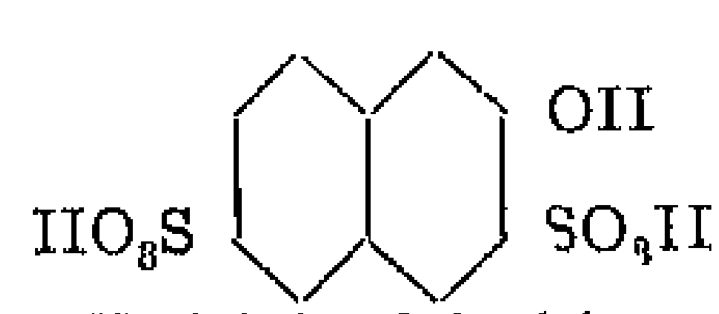
2-Naphthol-6-sulphonic acid (Schaffer's or β-acid)



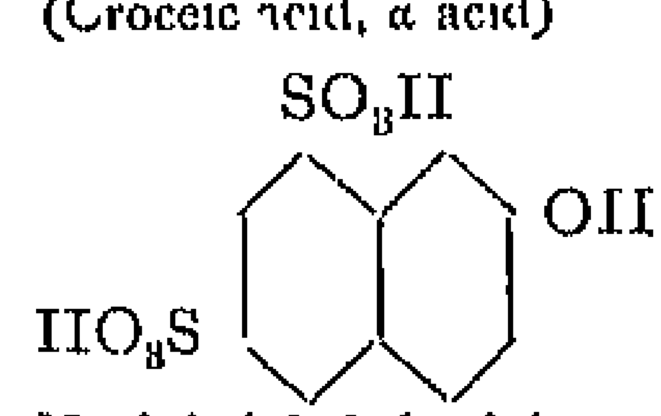
2-Naphthol-8-sulphonic acid (Croceic acid, α-acid)



1-Amino-8-naphthol-3:6-disulphonic acid (H-acid)



2-Naphthol-3:6-disulphonic acid (R-acid)



2-Naphthol-6:8-disulphonic acid (G-acid)

[1] For the behaviour of the naphthols on oxidation see R. Pummerer, *Ber.*, 1914, **47**, 2957; 1919, **52**, 1392. For the conversion of naphthol carboxylic acids into the aldehydes, see H. Weil and Heerdt, *Ber.*, 1911, **44**, 3058. [2] P. Friedländer, *Ber.*, 1921, **54**, 620; W. Fuchs and Stix, *Ber.*, 1922, **55**, 658.

Among the numerous sulphonic acids of the naphthols those named above are the ones chiefly used in the preparation of azo-dyes Nevile and Winther's acid and *disulphonic acids H, R and G* are of particular value The two last are formed by the vigorous sulphonation of β-naphthol and can be separated by taking advantage of the different solubilities of their acid sodium salts in alcohol, that of the G-acid being readily soluble and that of the R-acid almost insoluble Whereas 2-naphthol-8-sulphonic acid and G acid generally yield yellowish dyes when coupled with diazonium compounds, Schaffer's acid and R-acid give bluish dyes

In addition to the azo dyes described on p 405, the following derived from naphthol sulphonic acids and diazotised amines may also be mentioned

Crocein orange, $C_6H_5 \overset{1}{N}$ N $C_{10}H_5(\overset{2}{O}H)\overset{6}{S}O_3H$, from aniline and Schaffer's acid

Ponceau, from aniline and R acid

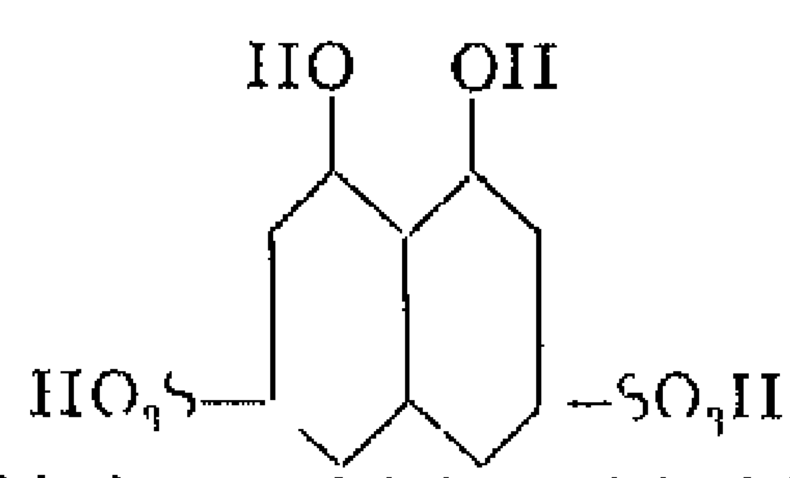
Bordeaux B, from α naphthylamine and R acid

Orange G, from aniline and G acid

Finally it should be noted that important dyes (such as **Roccellin**, SO_3H $C_{10}H_6$—N N—$C_{10}H_6OH$) are derived from *α naphthalene azo β naphthol*, $C_{10}H_7$—N N—$C_{10}H_6OH$, which is obtained by coupling diazotised α naphthyl amine with β naphthol

Sulphonic acids of α naphthol containing hydroxyl and sulphonic groups in the *peri* position (1 8) very readily split off water between the SO_3H and OH groups, with the formation of **sultones** 1 8 Naphthol sulphonic acid (Schöllkopf's acid) yields *naphtha-sultone*, $C_{10}H_6\left<\begin{matrix}SO_2\\|\\O\end{matrix}\right.$ the simplest compound of this type

A number of isomeric dihydroxy-naphthalenes are known, among which *peri*-**dihydroxy naphthalene** may be specially noted, since in consequence of the adjacent position of the two hydroxyl groups it resembles *o*-dihydroxy compounds in forming mordant dyes This property is utilised in azo-dyes prepared from a disulphonic acid of *peri*-dihydroxy-naphthalene, which are classed together under the name of **chromotrope** dyes The acid itself is consequently termed **chromotropic acid**

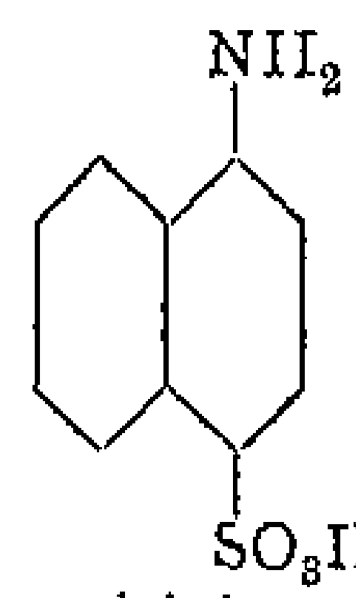


1 8 Dihydroxy naphthalene 3 6 disulphonic acid, chromotropic acid

The colours produced with azo dyes derived from this acid undergo surprising variations with change of metallic mordant For example, the dye prepared from diazotised aniline dyes wool in acid bath a red colour Aluminium salts transform this colour to violet and chromates to blue-black

α- and *β*-**Naphthylamines**, $C_{10}H_7 \cdot NH_2$, can be prepared by reducing the corresponding nitro-compounds, or from the naphthols by heating under pressure with ammonia In the presence of ammonium sulphite the latter reaction proceeds very readily *α-Naphthylamine*, m p 50°, b p 300°, is obtained on the large scale by reducing *α*-nitronaphthalene with iron and hydrochloric acid It possesses an unpleasant odour and is readily attacked by oxidising agents Aqueous solutions of its salts give a blue precipitate with ferric chloride *β-Naphthylamine*, m p 112°, b p 294°, is prepared technically by heating *β* naphthol in iron autoclaves with ammonia and zinc chloride It is odourless and gives no coloration with oxidising agents The naphthylamines and their sulphonic acids are largely employed in the manufacture of azo-dyes (see pp 405 and 527)

On treatment with fuming sulphuric acid, *α*-naphthylamine yields **naphthionic acid**, which corresponds to sulphanilic acid



1 4-Aminonaphthalene sulphonic acid,
naphthionic acid

When this compound is diazotised and coupled with *β*-naphthol, it is converted into **fast red A** Naphthionic acid coupled with tetrazobenzidine chloride forms **Congo red** (see p 405)

Among numerous amino naphthol-sulphonic acids we may mention 1-*amino-2-naphthol-6-sulphonic acid*, the sodium salt of which is used as a photographic developer under the name of **eikonogen**

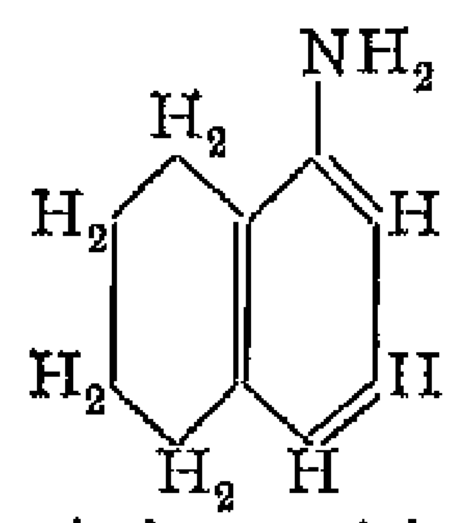
Hydrogenated Naphthylamines[1]

Each of the naphthylamines may be reduced to a tetrahydronaphthylamine by the use of sodium and amyl alcohol, all four hydrogen atoms entering the same benzene nucleus The compounds so obtained show striking differences in properties If hydrogenation takes place in the ring containing the amino-group, as is mainly the case with *β*-naphthylamine, the product possesses the character of an aliphatic amine, or rather of a phenyl-substituted aliphatic amine. This type of reduction is distinguished as aliphatic-cyclic or *alicyclic hydrogenation*, and the compounds formed are written with the prefix *ac* (alicyclic) If, on the other hand, reduction occurs in the unsubstituted benzene nucleus, as is chiefly the case with *α*-naphthylamine,

[1] E Bamberger, *Ann*, 1890, 257, 1 J v Braun, *Ber*, 1922, 55, 3664

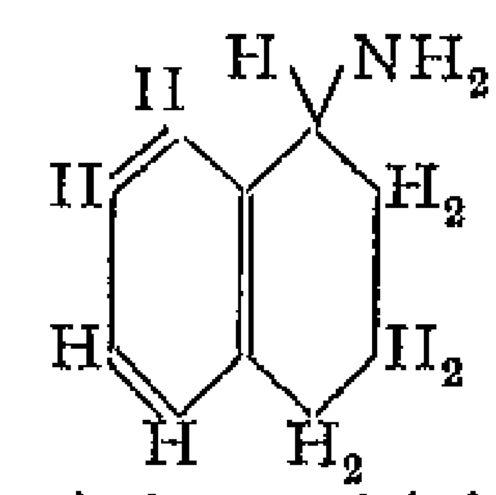
the product shows the properties of aniline and the aromatic bases. Hence reduction of this kind is termed *aromatic hydrogenation*, and the compounds are distinguished by the prefix *ar*. There are therefore four tetrahydro-naphthylamines known, the constitution of which may be expressed by the following formulæ:

I



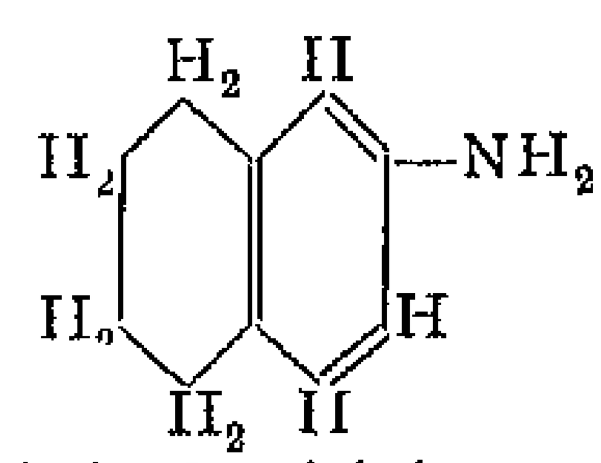
ar-Tetrahydro-α-naphthylamine

II



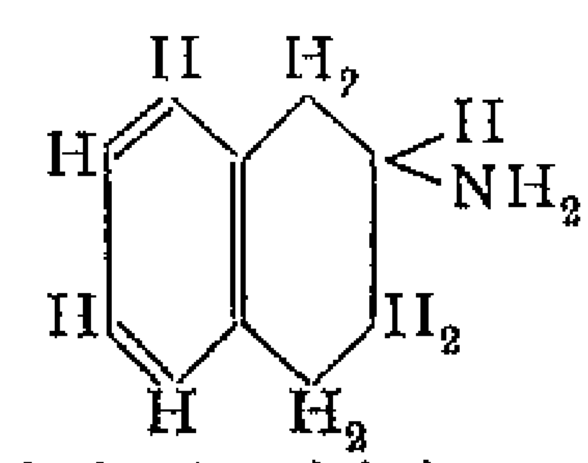
ac-Tetrahydro-α-naphthylamine

III



ar-Tetrahydro-β-naphthylamine

IV



ac-Tetrahydro-β-naphthylamine

That the hydrogen atoms always attach themselves asymmetrically, *i.e.*, to *one* of the two nuclei of the naphthalene molecule, was proved by Bamberger from an examination of the behaviour of the compounds with bromine and potassium permanganate. The above reduction products, for example, do not add on bromine at all, but if each nucleus had taken up two hydrogen atoms, then derivatives containing double bonds would have been formed which would have combined instantaneously with bromine.

The *behaviour of the ac-hydrogenated bases* (II and IV) indicates, as already stated, that these have altogether lost the aromatic character of the parent substance and have gone over completely to the aliphatic type. They are strong bases, which turn turmeric paper brown and form salts of neutral reaction. They have a sharp smell resembling that of piperidine and exert a peculiar physiological action. On standing in air they rapidly absorb carbon dioxide. In contact with diazo-compounds they yield aliphatic diazo-amino-compounds of the general formula $R—N_2—NHR$. Their behaviour with nitrous acid is very characteristic; unlike the aromatic bases they form no diazonium salts but give crystalline and readily soluble nitrites. Hence they can not be used for the preparation of dyes. When oxidised with potassium permanganate, the *ac*-tetrahydro-compounds, again unlike the *ar*-derivatives, are attacked in such a way that the reduced ring opens, and a benzene-dicarboxylic acid containing all the carbon of the original base is formed. Thus each of the *ac*-tetrahydro-

naphthylamines yields on oxidation *o-carboxy-hydrocinnamic acid*, $C_6H_4\!\left\langle\begin{matrix}CH_2\cdot CH_2\cdot COOH\\ COOH\end{matrix}\right.$

In distinction to the above *ac*-bases, *the aromatic hydrogenated bases* (I and III) do not greatly differ from the parent substances containing four hydrogen atoms less, so that they may be considered as almost purely aromatic in type. *ar*-Tetrahydro-*a*-naphthylamine possesses the properties of a substituted aniline: it does not affect vegetable dyes, does not easily react with carbon disulphide, and is readily diazotised with nitrous acid. When it is oxidised with permanganate the ring containing the amino-group is entirely removed, with the formation of *adipic acid*, $COOH\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot COOH$.

It is worthy of emphasis that the influence of alicyclic as well as of aromatic hydrogenation is not confined to the reduced ring, but also makes itself felt in the adjacent ring. This is shown in the enhanced aromatic character of the latter, bringing it into still closer resemblance to the ring of benzene derivatives. With reference to physical properties it may be noted that both the *ac*- and *ar*-hydrogenated bases have lower boiling-points than the parent amines, as will be seen from the following table.[1]

Parent Bases	Hydrogenated Compounds	
	Aromatic	Alicyclic
α-Naphthylamine 300°	Tetrahydro 275°	Tetrahydro 246.5°
β-Naphthylamine 299.5°	" 276.5°	" 249.5°
α-Ethyl-naphthylamine 303°	" 286-287°	" —
β-Ethyl-naphthylamine 305°	" 291.5°	" 267°
α-Dimethyl-naphthylamine 274.5°	" 261-262	" —
β-Dimethyl-naphthylamine 305°	" 287	" —

As already indicated on p. 529, the same regularities that have been observed in the case of the hydrogenated bases of naphthalene also hold true for the hydrogenated naphthols. The facts have been summed up by Bamberger as follows:—

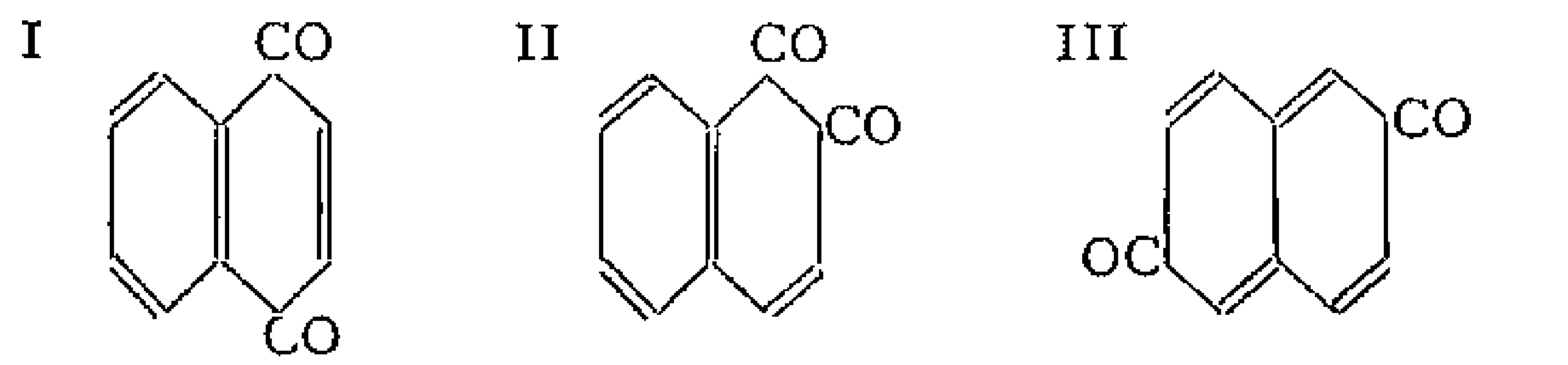
1. *When one of the two ring systems of naphthalene or its derivatives takes up four hydrogen atoms, this ring acquires the functions of an open aliphatic chain.*

2. *Such hydrogenation results in the reduced compound behaving as a benzene derivative with an aliphatic side chain. The hydrogenated portion of the molecule exhibits aliphatic properties, and the non-hydrogenated portion aromatic properties.*

[1] Bamberger, *Ber.*, 1889, **22**, 773.

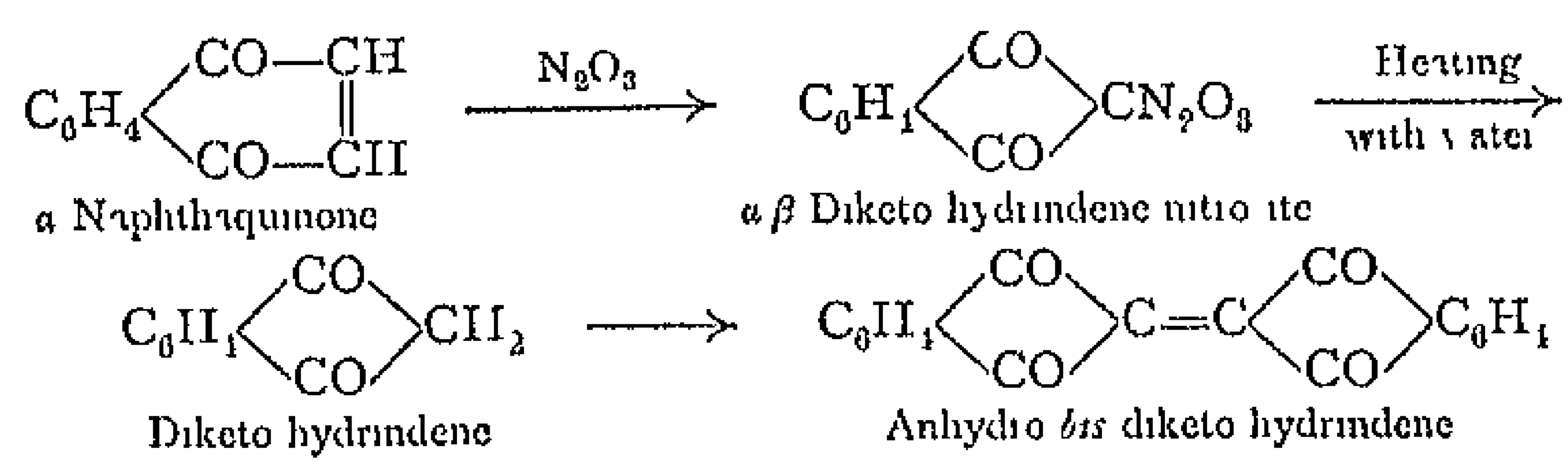
(d) *Naphthaquinones and Naphthalene Carboxylic Acids*

Three quinones of naphthalene are known, namely



α- or 1 4 β or 1 2 amphi or 2 6 naphthaquinone

α-Naphthaquinone corresponds to *p*-benzoquinone. It is prepared by oxidising naphthalene with chromic acid in boiling glacial acetic acid. Better yields are obtained by oxidation of 1 4-dihydroxy-naphthalene, or of 1 4-aminonaphthol. It is also formed when naphthalene, dissolved in acetone containing sulphuric acid, is electrolytically oxidised at a platinum or lead anode. In its properties it strongly resembles quinone. It crystallises from alcohol in yellow needles, m p 125°, has a pungent smell and is very volatile. Sulphurous acid reduces it to 1 4-*dihydroxy-naphthalene*, and with nitric acid it is oxidised to phthalic acid. Liquid nitrogen trioxide converts it into indene derivatives [1]



The above is an example of the remarkable syntheses of indene derivatives, in which a six-membered carbon ring is transformed into a five-membered ring. This change also results from the action of chlorine or hypochlorous acid on naphthols, naphthaquinones and other naphthalene compounds [2]

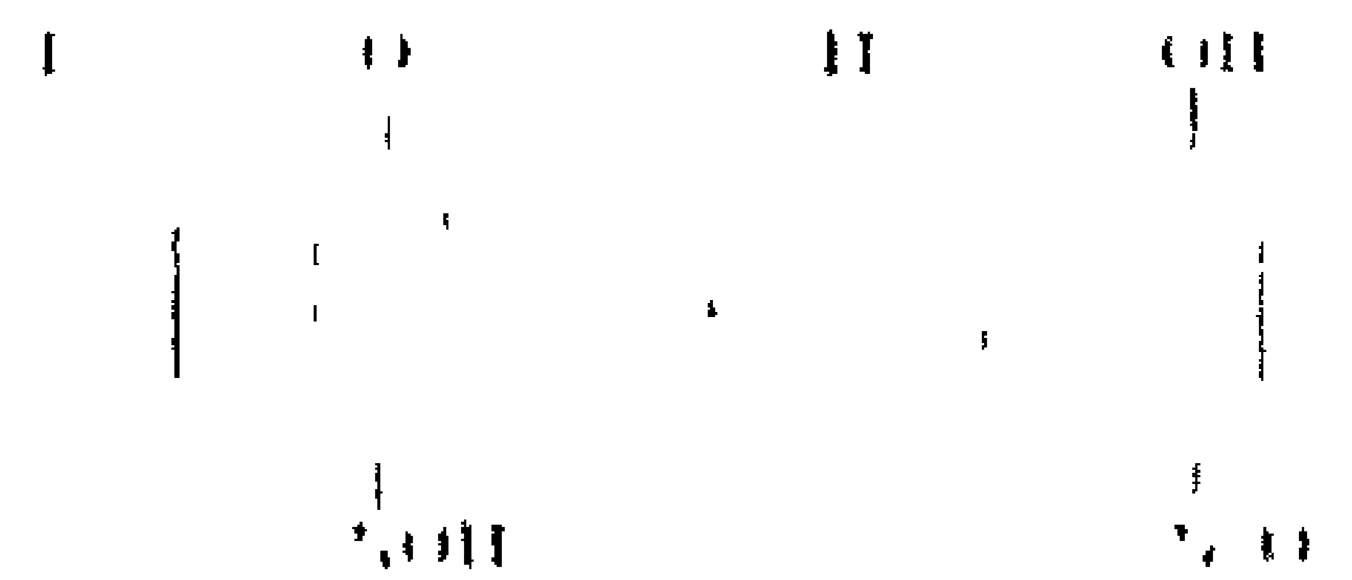
Carminic acid, the colouring matter of the cochineal insect (*Coccus cacti*), and **kermic acid**, the dye-stuff of *Coccus ilicis*, appear to be derivatives either of α-naphthaquinone or of anthracene [3]

β-Naphthaquinone, which may be compared to *o*-benzoquinone, results from the oxidation of 1 2-amino-naphthol. It crystallises in red needles which decompose about 120°. It differs from the α-compound in being odourless and non-volatile. In chemical behaviour it resembles anthraquinone and even more closely phenanthraquinone. As will be seen later, the reactions of the latter are those of an

[1] J Schmidt, *Ber*, 1900, 33, 543 [2] Zincke, *Ber*, 1887, 20, 2890, 3216; 1888, 21, 2379, 2719; 1889, 22, 1024, 2316. [3] O Dimroth, *Ber*, 1910, 43, 1387; *Ann*, 1913, 399, 1.

ortho-diketone [illegible] sulphurous acid reduces β-naphthaquinone to 1 : 2-dihydroxynaphthalene.

When treated in alcoholic solution with hydroxylamine hydrochloride the naphthaquinones are converted into [illegible] oximes. These are identical with the compounds obtained by the action of nitrous acid on the naphthols, hence they may also be



[illegible]

considered as nitrosonaphthols. Here we have a case of tautomerism analogous to that of the nitrosophenols.[1] The [illegible] one or more.

The [illegible] of β-naphthaquinone differ from those of α-naphthaquinone in their ability to [illegible] dark green lakes with ferric oxide. In particular the [illegible] nitroso-β-naphthol-sulphonic acid [illegible] under the name of Naphthol Green. [illegible] naphthol precipitates various metals from their solutions, cobalt for example, [illegible] cobalt compound which may be utilised in separating nickel and cobalt.

Amphi-naphthaquinone (formula [illegible]) is formed when 2 : 6-dihydroxynaphthalene, suspended in benzene, is oxidised with lead peroxide.[2] It crystallises in small yellowish-red prisms and is very unstable toward water, dilute acids and alkalis. In physical properties it resembles the o-quinones. Like the benzoquinones it is distinguished by a tendency to change into the [illegible].

The *amphi*-compound differs from α- and β-naphthaquinone in its far stronger oxidising action. It is truly naphthaquinonoid, whereas the α- and β-isomerides are not completely quinonoid in structure. Here a distinction is drawn between quinones in which the benzene ring or condensed double ring of naphthalene is completely quinonoid and those in which a quinonoid double bond is also part of an aromatic nucleus.

In formation and properties the *naphthalene carboxylic acids* resemble the corresponding acids of benzene, to which reference should be made.

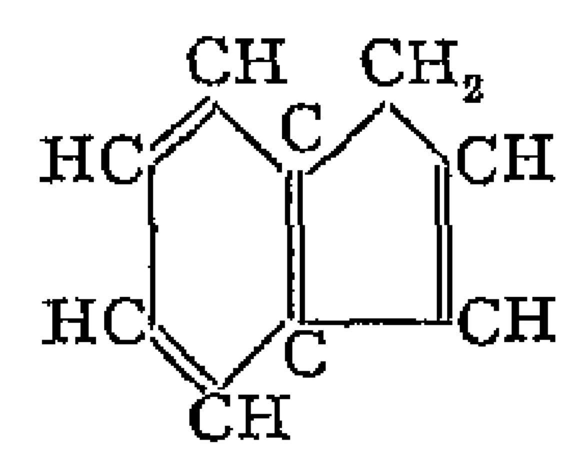
α-**Naphthoic acid**, naphthalene-α-carboxylic acid, $C_{10}H_7 \cdot COOH$, is formed by the action of carbon dioxide on naphthyl magnesium bromide. It melts at 160°, and at higher temperatures loses carbon

[1] C. H. [illegible], [illegible], 44, [illegible]. [2] R. Willstätter and J. Parnas, *Ber.*, 1907, 40, 1406.

dioxide to yield naphthalene *β*-**Naphthoic acid** melts at 182° **Naphthalic acid**, naphthalene 1 8 dicarboxylic acid, $C_{10}H_6(COOH)_2$, when heated to a high temperature yields an anhydride resembling phthalic anhydride

Among other derivatives of naphthalene may be mentioned **acenaphthene** or *peri*-ethylene-naphthalene, $C_{10}H_6\left\langle\begin{matrix}CH_2\\ | \\ CH_2\end{matrix}\right.$, m p 95°, b p 277°, which is found in coal tar[1] It may be prepared by treating *α*-bromoethyl-naphthalene, $C_{10}H_7$ CH_2 CH_2Br, with alcoholic potash

Indene —As will be seen from the annexed formula, indene contains a benzene nucleus condensed with a cyclo-pentadiene ring It is present in coal tar, and may be isolated from the "heavy oil" by fractionation and subsequent precipitation with picric acid[2] A simpler method is to heat the crude indene with sodium at 140° to 150°, when **sodium indene** is formed as a glassy mass This on treatment with water yields very pure indene[3] It is a colourless oil, b p 178°



Indene

$$C_6H_4\left\langle\begin{matrix}CH{=\!=}\\ CHNa\!-\end{matrix}\right\rangle CH$$

Indene and its derivatives may be obtained synthetically by a number of reactions (see p 531) Thus *o*-xylylene bromide and sodio-malonic ester combine to form *hydrindene dicarboxylic ester*,

$$C_6H_4\left\langle\begin{matrix}CH_2Br\\ CH_2Br\end{matrix}\right. + Na_2C(COOR)_2 = C_6H_4\left\langle\begin{matrix}CH_2\\ CH_2\end{matrix}\right\rangle C(COOR)_2 + 2NaBr$$

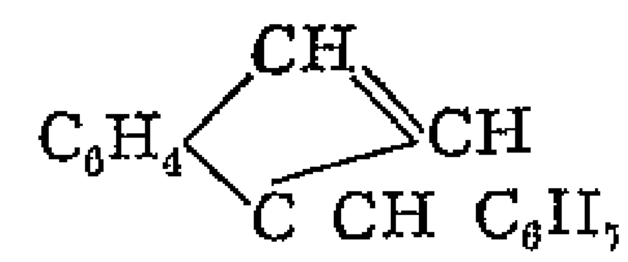
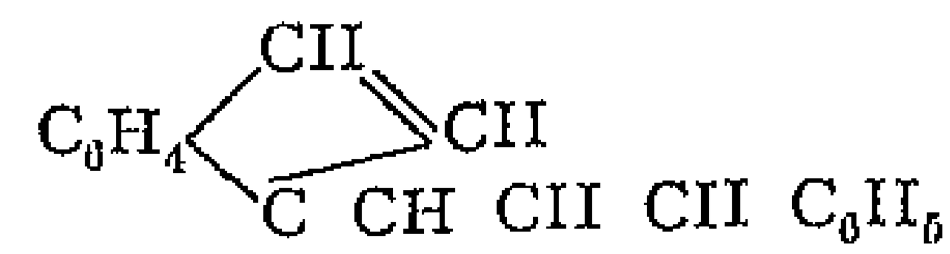
which by hydrolysis and elimination of carbon dioxide can be converted into *hydrindene carboxylic acid* When the barium salt of the latter is distilled it yields indene[4]

$$C_6H_4\left\langle\begin{matrix}CH_2\\ CH_2\end{matrix}\right\rangle CH\ COOH \longrightarrow C_6H_4\left\langle\begin{matrix}CH\\ CH_2\end{matrix}\right\rangle CH + CO_2 + H_2$$

The chief properties of indene depend on the reactivity of the two hydrogen atoms of the CH_2-group (*cf* fluorene) When indene is heated with alkyl halides in the presence of alkali, these hydrogen atoms are replaced by alkyl groups, and in the condensation of indene with aldehydes they unite with the aldehydic oxygen to form water[5]

[1] For acenaphthene quinone, see A Reissert, *Ber.*, 1911, 44, 1749 [2] Kramer and Spilker, *Ber*, 1890, 23, 3276, Weger and Billmann, *Ber*, 1903, 36, 641 [3] Weiszgerber, *Ber*, 1909, 42, 569, 1911, 44, 1436 [4] For the preparation of indene derivatives from phthalic aldehyde, see J Thiele and Falk, *Ann*, 1906, 347, 112, and from unsaturated ketones, Thiele and Ruggli, *Ann*, 1912, 393, 61 [5] For further details see Thiele, *Ann*, 1906, 347, 249

In this manner benzaldehyde and indene yield *benzylidene-indene* (I) and hydroxy-benzyl-indene, while cinnamic aldehyde and indene give *cinnamylidene indene* (II)

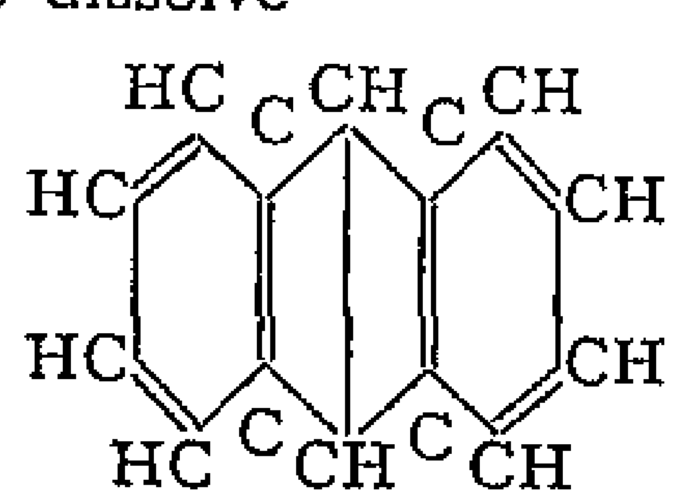
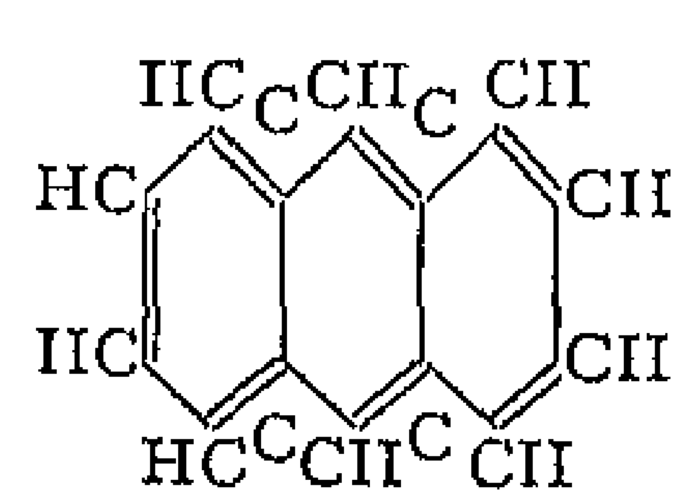
I  II 

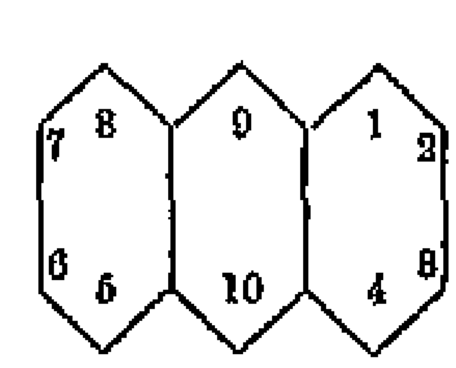
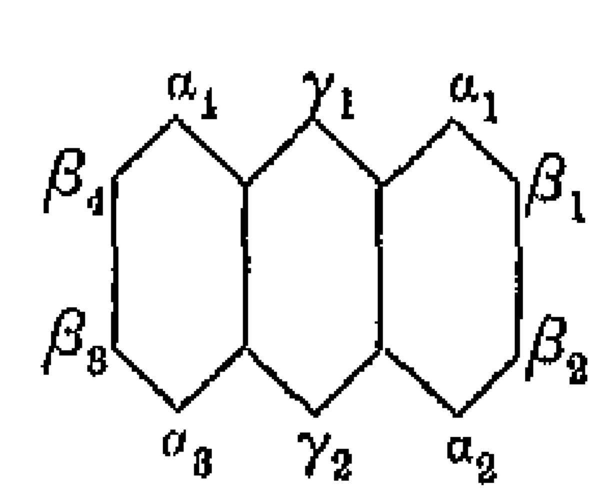
Indene readily takes up oxygen from the air and has a strong tendency to polymerise With nitric acid it is oxidised to phthalic acid, and on reduction with sodium and alcohol, or more simply by catalytic hydrogenation,[1] it is converted into *hydrindene*, C_9H_{10}

XV

Anthracene Group

Anthracene, $C_{14}H_{10}$, is the parent substance of a number of interesting compounds and valuable dye-stuffs It is present to the extent of 0 25 to 0 45 per cent in coal tar, and distils over in the anthracene oil, boiling above 270° In this it is mixed with various products such as phenanthrene, chrysene, carbazole and paraffins, which are difficult to remove Crude anthracene crystallises out from the mixture on cooling and is separated in filter presses The product, which contains about 30 to 50 per cent of anthracene, is purified by treatment with pyridine bases or solvent naphtha, when most of the phenanthrene, fluorene and other impurities pass into solution, leaving an 80 to 90 per cent anthracene The latter is obtained in finely-divided form by sublimation or distillation in steam, and if required for the preparation of dyes is then worked up directly into anthraquinone Commercial crude anthracene may be further purified in a number of ways, *e g* by treatment with liquid sulphur dioxide, in which the impurities dissolve

I  II 

II*a*  II*b* 

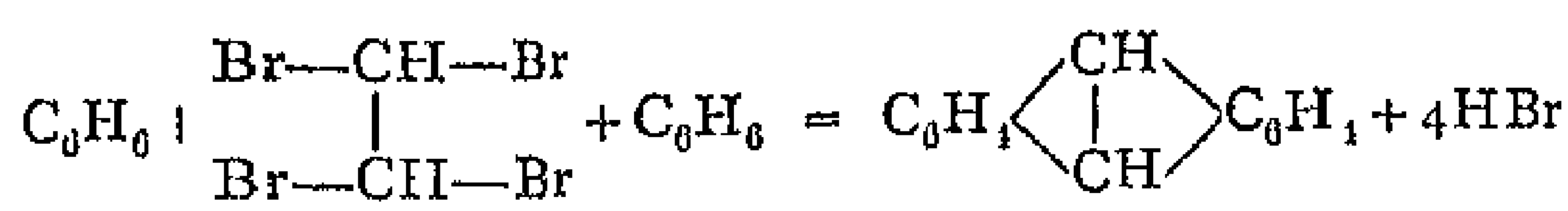
[1] J v Braun and Kirschbaum, *Ber*, 1922, 55, 1680

Pure anthracene, m p 213°, b p 351°, crystallises in colourless plates having a blue fluorescence It dissolves readily in hot benzene, with difficulty in alcohol and ether, and is insoluble in water Picric acid combines with it to form an addition compound, $C_{14}H_{10}, C_6H_2(NO_2)_3OH$, crystallising in red needles, m p 138° According to Graebe and Liebermann the constitution of anthracene is represented by formula I As will be seen, this is built up of three condensed benzene nuclei, the central one containing a para-linkage

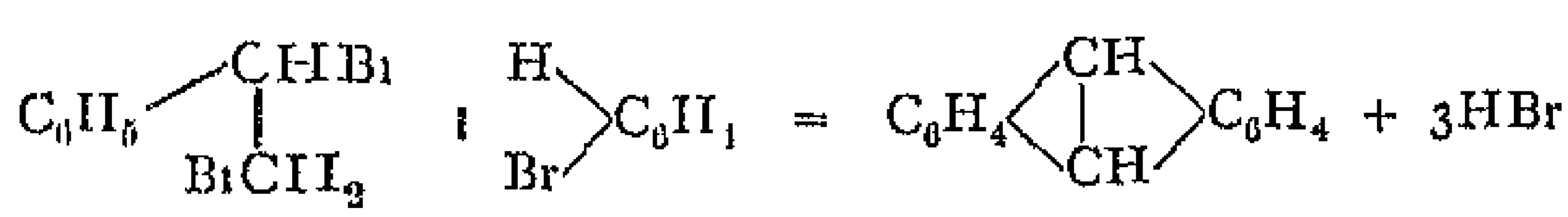
This structure is supported by the results of analysis and synthesis Recently the "ortho-quinonoid" formula II has been taken more and more into consideration[1]

Anthracene is formed by the following reactions

1 By heating benzene with symmetrical tetrabromo-ethane in the presence of aluminium chloride (Anschutz),

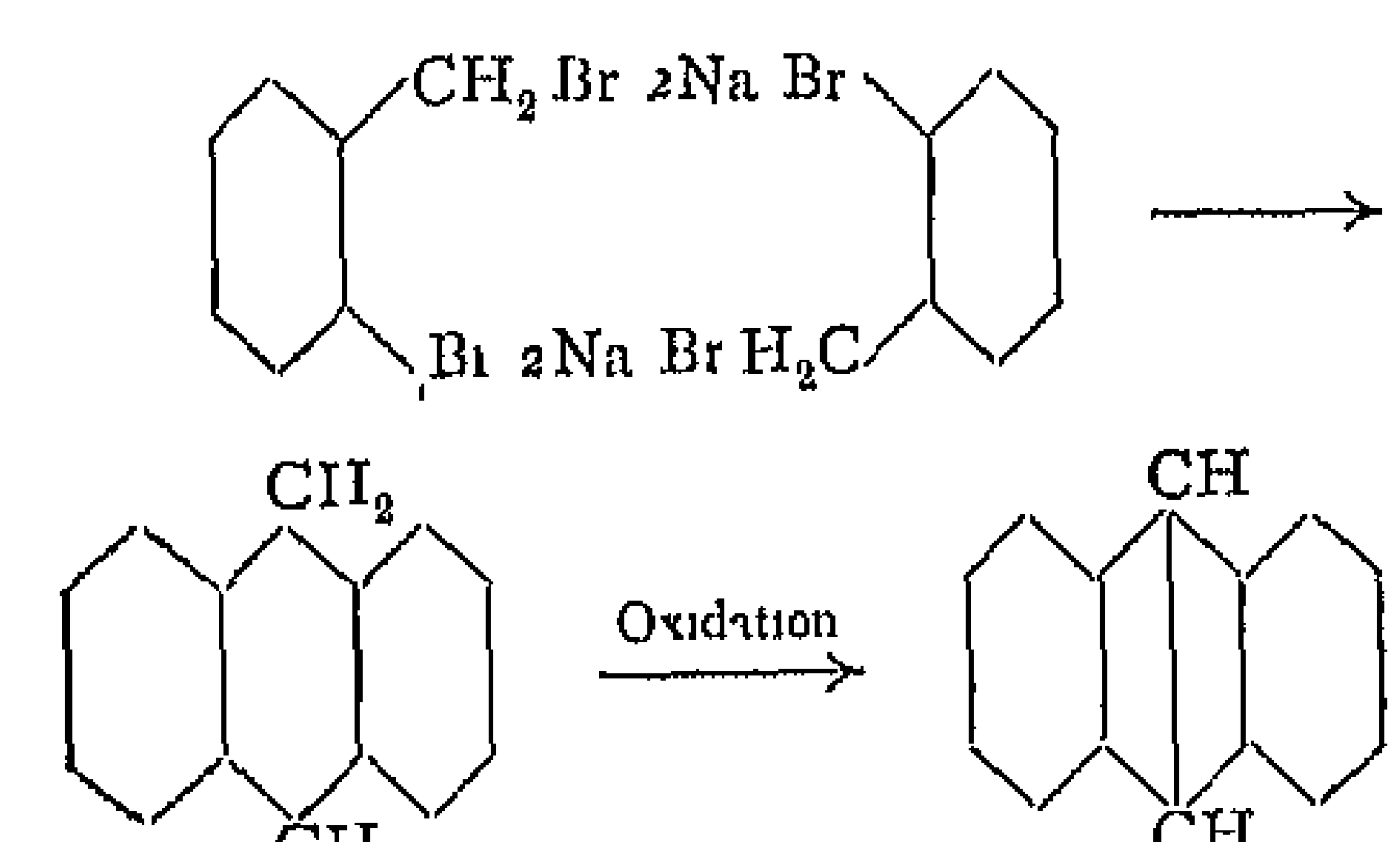


2 In a similar manner, by the action of aluminium chloride on a mixture of $\alpha\beta$-dibromo-ethyl-benzene and bromo benzene[2]



These two syntheses prove that the middle group, C_2H_2, of anthracene is linked to two benzene nuclei, but give no information as to the actual points of union

3 Anthracene, however, is also formed when o-bromo-benzyl bromide is treated with sodium Hence it follows that the middle group is attached to two o-carbon atoms of each benzene ring In this reaction the first product is dihydro-anthracene, which is readily converted into anthracene by oxidation

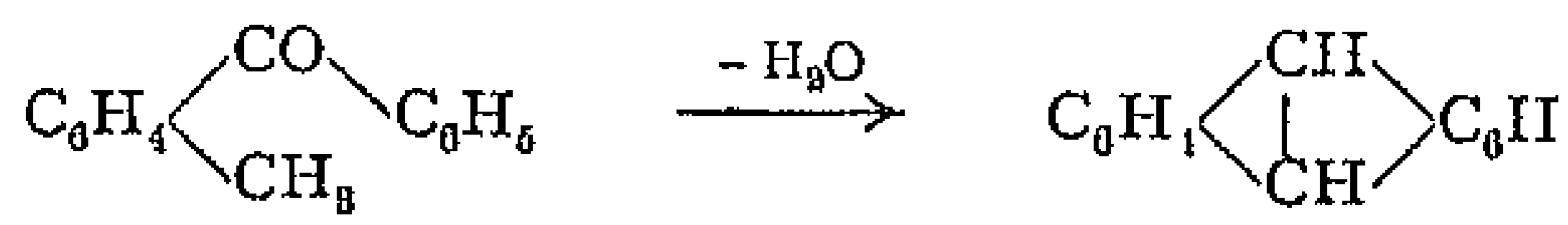


Dihydro-anthracene Anthracene

[1] K. v. Auwers, *Ber.*, 1920, 58, 941; 1925, 58, 543

[2] Schramm, *Ber.*, 1893, 26, 1706

4 Anthracene is also obtained by heating *o*-tolyl phenyl ketone with zinc dust



A number of other syntheses of anthracene have also been effected Synthetic methods of preparing anthraquinone, and the formation of anthracene from this compound and from alizarin, are described later

Derivatives of Anthracene

Anthracene[1] behaves in the same manner as naphthalene on *hydrogenation* Reduction with sodium and alcohol results in the addition of two hydrogen atoms to the "middle group," with formation of *dihydro-anthracene* Energetic reduction with phosphorus and hydriodic acid yields *hexahydro-anthracene*, $C_{14}H_{16}$, and *anthracene perhydride*, $C_{14}H_{24}$ Catalytic hydrogenation under pressure leads to the production of *octahydro-anthracene*, $C_{14}H_{18}$, m p 73°, which is also readily prepared on the technical scale[2]

Numerous substitution products of anthracene are known, the position of the substituents being indicated by numbers or letters as given in formulæ II*a* and II*b* on p 534 These formulæ also illustrate the large number of structural isomerides possible Substitution in the middle group leads to the formation of γ- or *meso*-derivatives According to theory there should be three isomeric monosubstitution products in every case Only the most important of these compounds will be described here

The action of chlorine or bromine on anthracene leads first to the formation of *γ-mono- and di-halogen* derivatives

Nitric acid very readily oxidises anthracene to *anthraquinone* On the other hand, nitric acid reacts with anthracene in glacial acetic acid solution in the presence of acetic anhydride to form 9-*nitro anthracene* This compound is more conveniently prepared by an indirect method described later

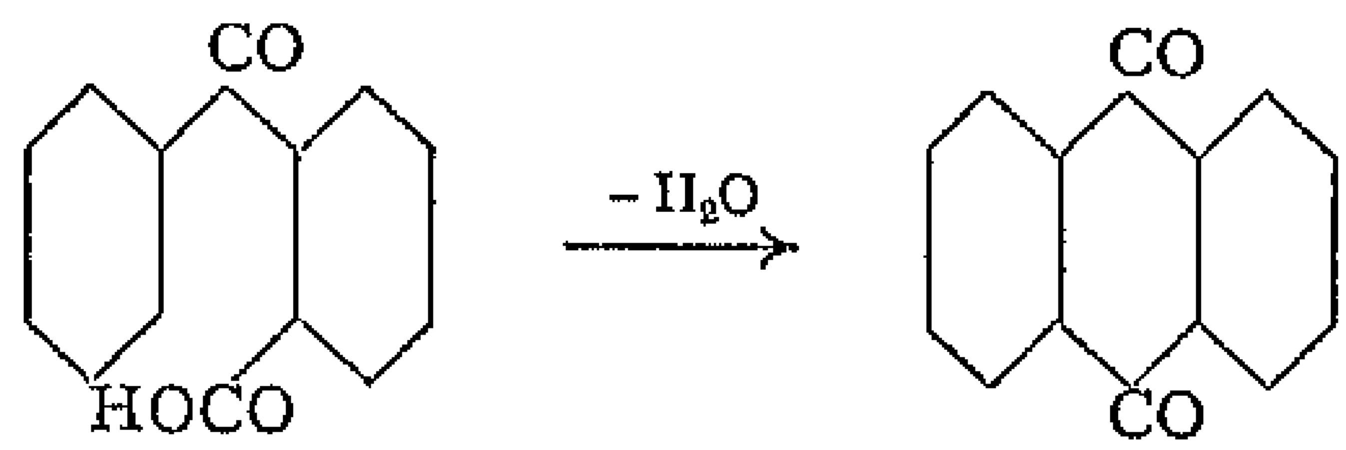
Anthracene-sulphonic acids can be obtained by the sulphonation of anthracene, or by the reduction of anthraquinone-sulphonic acids

Hydroxy-anthracenes, which resemble the phenols and naphthols in their behaviour, are formed by fusing anthracene-sulphonic acids with alkali, and by the reduction of anthraquinone and its substitution products The meso-phenols of the anthracene series, *anthranol* and *anthra-hydroquinone*, exhibit tautomerism[3]

Anthraquinone, $C_6H_4(CO)_2C_6H_4$, is obtained synthetically when *o*-benzoyl-benzoic acid is heated with phosphorus pentoxide This

[1] For a synthesis of anthracene from a naphthalene derivative, see W A Noyes and Colver, *J Am. C S*, 48, 898 [2] G Schroeter, *Ber*, 1924, 57, 2003, 1927, 60, 2035. [3] K H Meyer, *Ann.*, 1911, 379, 37

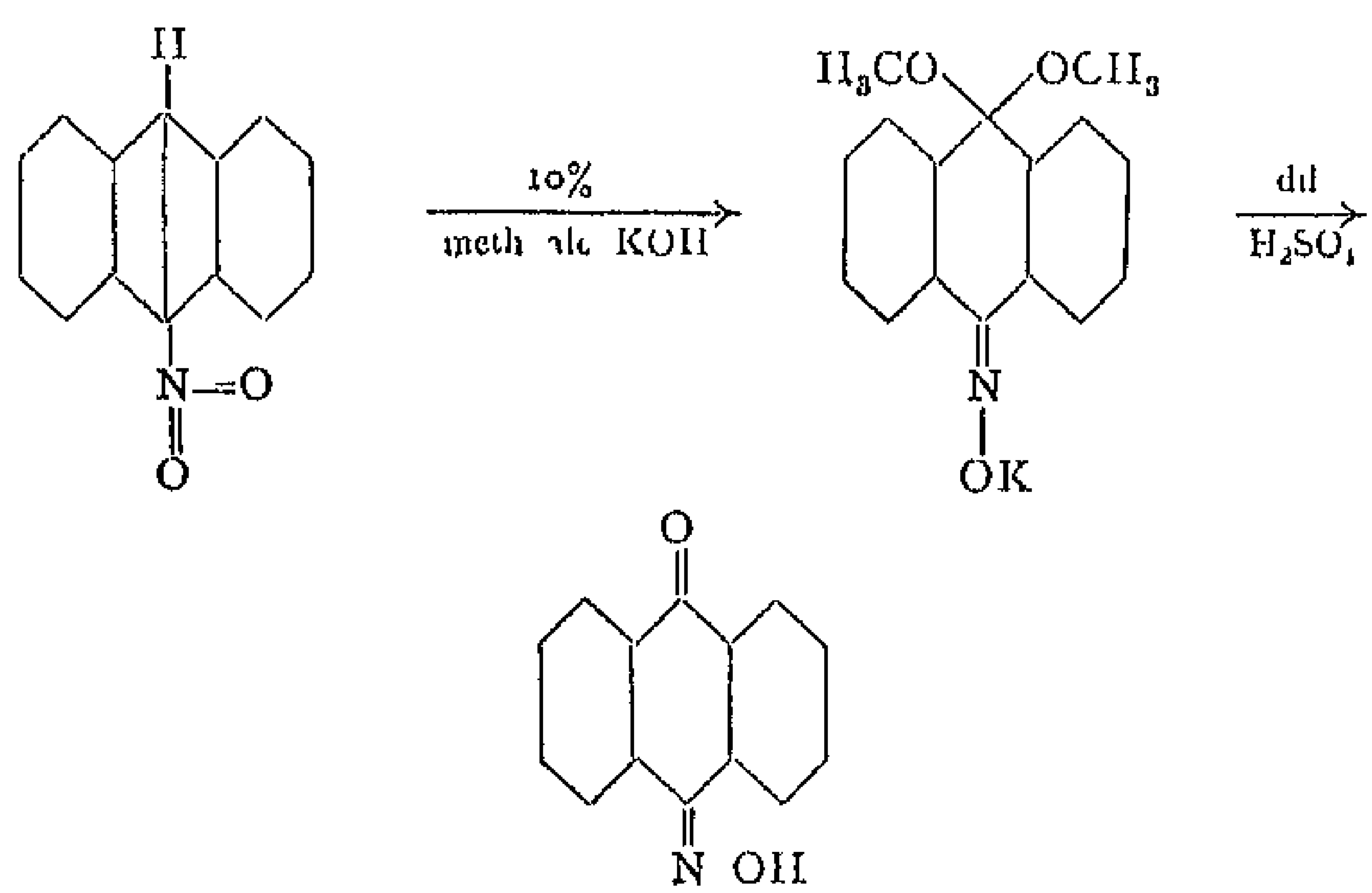
acid can be prepared by heating phthalic anhydride with benzene and aluminium chloride, or by the action of phenyl magnesium bromide on phthalic anhydride



o Benzoyl benzoic acid Anthraquinone

Anthraquinone is prepared industrially in large quantities for the manufacture of alizarin, by oxidising 90 per cent anthracene with sodium bichromate and sulphuric acid The product so obtained may be freed from impurities derived from the phenanthrene, fluorene, etc, present in crude anthracene, by dissolving it in hot concentrated sulphuric acid, in which anthraquinone dissolves unchanged while the original impurities or their oxidation products are converted into water-soluble sulphonic acids Hence, on diluting the acid solution with water, only anthraquinone is precipitated It may be further purified by distillation in steam or by treatment with pyridine

Anthraquinone melts at 285°, boils at 382°, and crystallises in yellow needles or prisms which readily sublime It is a very stable compound, and is only attacked with difficulty by nitric acid and oxidising agents In its whole behaviour it stands much closer to the diketones than to the quinones, possessing neither the characteristic pungent smell of quinone nor its property of being reduced to hydroquinone with sulphurous acid With hydroxylamine it yields bright yellow needles of *anthraquinone oxime*, which decompose at 224° According to



Anthraquinone oxime

Meisenheimer,[1] the oxime is also formed from 9-nitro-anthracene by boiling with methyl alcoholic potash and subsequent treatment with dilute mineral acid (*cf* p 525)

This reaction is of general significance in so far that the "*oxime transformation*" of α-unsaturated nitro-compounds under the influence of alkali appears to be a comparatively common property of this class of compound

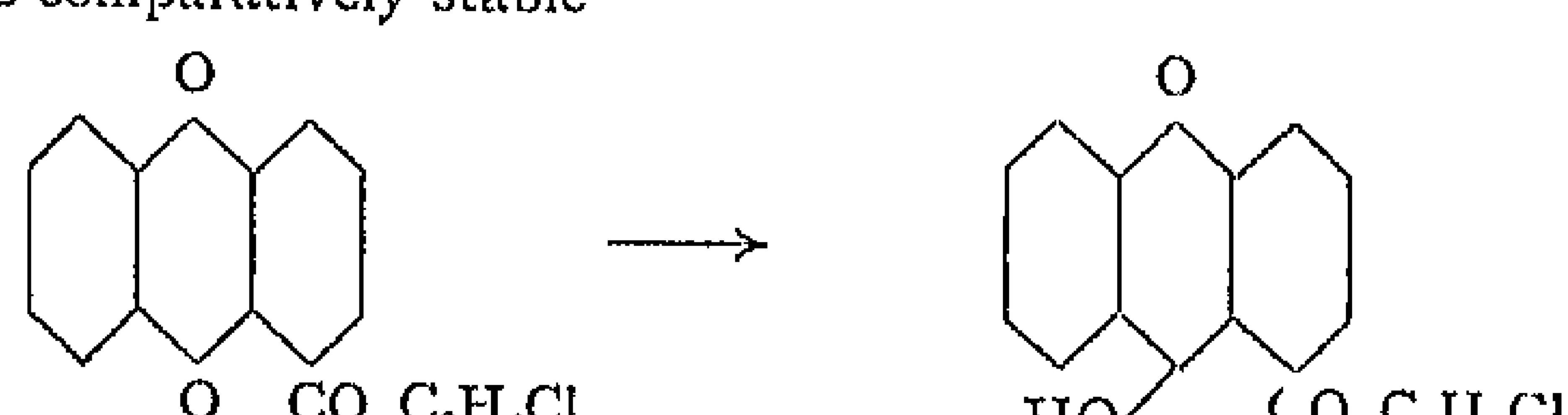
On fusion with potassium hydroxide anthraquinone breaks up to give two molecules of benzoic acid When reduced by warming with zinc dust and alkali it yields **anthrahydroquinone**, and by milder reduction with the same reagents, **oxanthranol**, $C_6H_4\left<\begin{matrix}CHOH\\CO\end{matrix}\right>C_6H_4$ The latter is an unstable substance which gives a beautiful and striking reaction sometimes used as a *test for anthraquinone* The greenish-yellow compound dissolves in alkali, giving a blood-red colour, on shaking with air, however, the red solution is very rapidly decolorised and yellow anthraquinone separates The alkaline solution has been shown to contain a considerable amount of hydrogen peroxide (or alkali peroxide)[2]

More vigorous reduction of anthraquinone with tin and hydrochloric acid yields **anthranol**, $C_6H_4\left<\begin{matrix}C(OH)\\|\\CH\end{matrix}\right>C_6H_4$, and with zinc dust and sodium hydroxide under pressure, **dianthranol**[3] Finally, by heating with phosphorus and hydriodic acid in a closed tube, or by distillation with zinc dust, anthracene may be obtained

Anthraquinone can be brominated, nitrated and sulphonated

Oxanthronyls Compounds containing Trivalent Carbon

When α-benzoylated anthraquinones are treated with aluminium or copper in concentrated sulphuric acid, or with zinc dust and ammonia, they are converted into remarkable compounds distinguished by a deep, violet-blue colour, and the magnificent fluorescence of their solutions in certain organic solvents These compounds, which have been termed *benzoyl oxanthronyls*, represent a new class containing trivalent carbon and are comparatively stable[4]



1-*p* Chlorobenzoyl anthraquinone 1-*p* Chlorobenzoyl 9 oxanthronyl

[1] *Ann*, 1902, **323**, 205, 1907, **355**, 249 [2] Manchot, *Ann*, 1901, **314**, 179 [3] H Meyer, *Ber*, 1909, **42**, 143 [4] R Scholl, *Ber*, 1921, **54**, 2376, 1925, **58**, 918, 1065, 1633

They are insoluble in alkali, form deep green sulphates with concentrated sulphuric acid, and their solutions gradually become decolorised on long standing in air and light, particularly in the presence of water. With alkaline hydrosulphite they undergo further reduction.

There are now several classes of compounds known containing trivalent carbon, including the *triaryl-methyls* discovered by Gomberg, the *metallic ketyls* of Schlenk, and the above *benzoyl-oxanthronyls*.

Anthraquinone Sulphonic Acids

The sulphonation of anthraquinone provides a striking illustration of the manner in which the course of a reaction may at times be influenced by the addition of an apparently indifferent substance (compare p. 442, on the conversion of naphthalene into phthalic acid). Sulphonation in the ordinary way only yields β-sulphonic acids, together with an exceedingly small quantity of α-acids. On the other hand, the presence of a small amount of mercury so favours the formation of α-sulphonic acids, that the product of reaction is almost pure α-acid. This action of mercury practically brings about a complete displacement of the normal position of substitution, and also enables the reaction to be carried through much more easily. It is therefore of great value industrially since anthraquinone sulphonic acids are important intermediate products in the preparation of dye-stuffs.

The catalytic influence of mercury does not appear to be limited to sulphonation, but extends to nitration and probably also to other substitution reactions of anthraquinone. So far as has been observed, however, this effect is peculiar to anthraquinone derivatives.

Another method of preparing α-anthraquinone sulphonic acids is to heat α-nitro-anthraquinones with aqueous solutions of neutral alkali sulphites, when the nitro-group is readily exchanged for the sulphonic group. Thus α-nitro-anthraquinone yields *anthraquinone α-sulphonic acid*, and the 1 5- and 1 8-dinitro-derivatives give the corresponding 1 5- and 1 8-*disulphonic acids*. In these α-sulphonic acids the acid group is comparatively reactive. When heated with milk of lime they are converted into *hydroxy-anthraquinones*, and with ammonia or primary amines they yield the corresponding *amino-anthraquinones*. On being heated with potassium phenoxide the α-sulphonic acids yield *phenyl ethers of hydroxy-anthraquinones*. Reduction with zinc dust and ammonia converts anthraquinone-α-monosulphonic acid into *anthracene-α-sulphonic acid*, which on fusion with alkali gives *α-anthrol*. The nitration of anthraquinone α-sulphonic acid leads to the formation of two *nitro-anthraquinone sulphonic acids*, with the substituents in the 1 5- and 1 8-positions respectively. These are readily reduced to 1 5- and 1 8 *amino anthraquinone*

sulphonic acids, which can be diazotised and coupled with phenols and amines. When heated with methylamine these amino-acids exchange the sulphonic group for the residue $—NH.CH_3$, with the production of 1.5- and 1.8-*monomethyl-diamino-anthraquinones*, $C_{14}H_{10}O_2\left<\begin{matrix}NH.CH_3\\NH_2\end{matrix}\right.$ It is obvious that a great number of anthraquinone derivatives can be prepared by such methods.

Hydroxy-anthraquinones

Hydroxy-anthraquinones can also be prepared from chloro- and bromo-anthraquinones by fusion with alkali, and further by the anthraquinone synthesis mentioned on p. 537, using phenols in place of benzene, *i.e.*, by heating phthalic anhydride with mono- or dihydric phenols in the presence of aluminium chloride. A reaction of practical value is the formation of polyhydroxy-anthraquinones by oxidising anthraquinone or its simple hydroxy derivatives by means of hot fuming sulphuric acid. The addition of a little boric acid considerably increases the yield.

Alizarin, 1.2-*dihydroxy-anthraquinone*, $C_{14}H_6O_2(OH)_2$, is the most important hydroxy derivative. It ranks with indigo as the most valuable of all dye-stuffs, whether synthetic or natural. Prior to 1869 it was exclusively prepared from madder root. *Madder* (Rubia tinctorum) is a shrub growing to about three feet in height, which was cultivated more especially in France. It contains in its root a number of glucosides such as rubian, rubianic acid, and ruberythric acid, $C_{26}H_{28}O_{14}$. On fermentation, or on hydrolysis, *e.g.* with hot dilute sulphuric acid, these yield a mixture of glucose and the dye-stuffs alizarin, $C_{14}H_6O_2(OH)_2$, and purpurin, $C_{14}H_5O_2(OH)_3$.

$$\underset{\text{Ruberythric acid}}{C_{26}H_{28}O_{14}} + 2H_2O = \underset{\text{Glucose}}{2C_6H_{12}O_6} + \underset{\text{Alizarin}}{C_{14}H_6O_2(OH)_2}$$

For dyeing, the ground-up root containing about 1 per cent of dye-stuff, or the prepared mixture of dyes (garancin), used to be employed.

Constitution of Alizarin.—In 1865 Graebe and Liebermann obtained the hydrocarbon anthracene by distilling natural alizarin with zinc dust. This fact, together with the discovery of the method described below of preparing alizarin artificially, pointed to the compound being an anthraquinone derivative in which two hydrogen atoms were replaced by two hydroxyl groups. The formation of phthalic acid by the oxidation of alizarin[1] proved that both hydroxyl groups were contained in the same benzene nucleus, and the synthesis of alizarin

[1] For the oxidation of alizarin in alkaline solution, see R. Scholl, *Ber.*, 1918, 51, 1419; 1919, 52, 1142, 1829.

from phthalic anhydride and pyrocatechol showed them to be in the *o*-position to one another

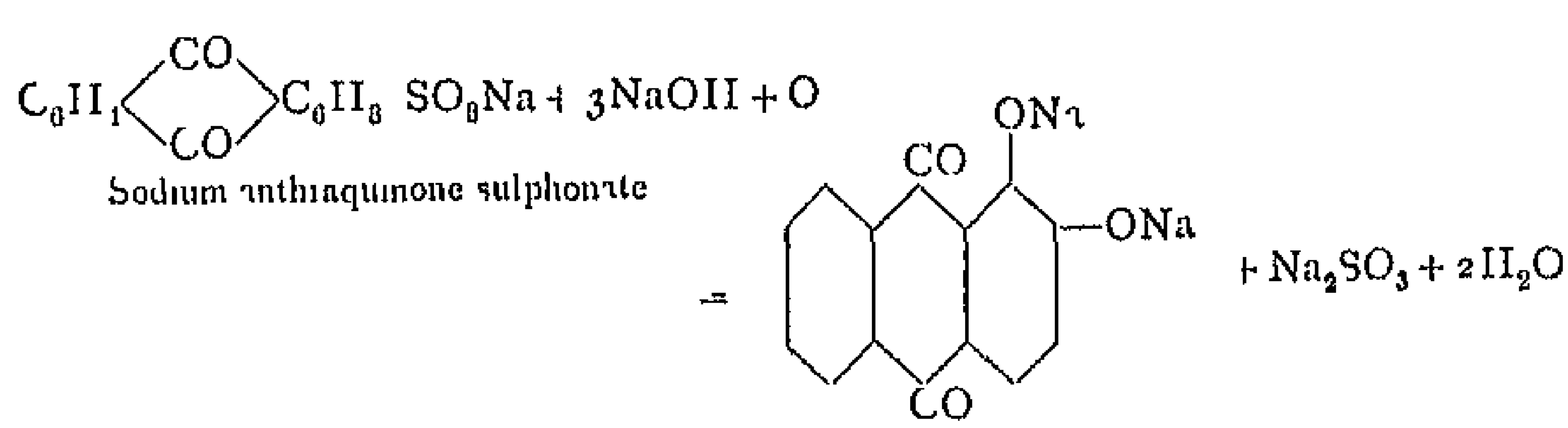
$$C_6H_4{<}^{CO}_{CO}{>}O + C_6H_4{<}^{OH[1]}_{OH[2]} = C_6H_4{<}^{CO}_{CO}{>}C_6H_2{<}^{OH}_{OH} + H_2O$$

Phthalic anhydride — Pyrocatechol — Alizarin

Finally, the existence of two isomeric nitro-alizarins having the nitro-group in the same benzene nucleus as the hydroxyl groups is a proof that the hydroxyl groups occupy the 1 2- and not the 2 3-position

Technical Preparation of Alizarin—Graebe and Liebermann were the first to prepare alizarin artificially They obtained it by fusing dibromo-anthraquinone with potassium hydroxide, a method not adapted to large scale practice The industrial preparation was only established successfully when Caro and Perkin substituted the cheaper anthraquinone sulphonic acids for the expensive dibromo-anthraquinone The process is carried out in the following manner

Equal amounts of anthraquinone and 40 per cent oleum are heated at 160° to 170°, in an iron vessel provided with stirring apparatus, when the greater part of the anthraquinone is converted into the β-mono-sulphonic acid (see above) On pouring the melt into water any unchanged anthraquinone separates out This is filtered off, and the sulphonic acid is precipitated from the filtrate as the sparingly soluble sodium salt by the addition of soda The salt is then fused with sodium hydroxide and the requisite amount of potassium chlorate Under these conditions, one hydroxyl group is introduced in place of the sulphonic group and a second one is formed by direct oxidation



Sodium salt of alizarin

The fusion is effected under pressure in horizontal iron cylinders provided with stirring, at about 180° to 185° The fused mass is dissolved in water and alizarin precipitated as orange yellow flakes by the addition of sulphuric acid It is separated in filter presses, mixed with water to a 20 per cent paste and placed in this form on the market

100 parts of coal tar containing 0 6 parts of anthracene yield 0 6 parts of alizarin

The artificial preparation of alizarin was the first synthesis of a

valuable natural dye-stuff to be successfully carried out on the industrial scale. Synthetic alizarin has completely displaced the natural product from the market, and has not only led to the decay of madder cultivation in the Mediterranean countries, but has brought about great changes in the occupation of the people in these parts. Districts which used annually to produce valuable supplies of madder have now reverted to ordinary agricultural pursuits.

Properties and Use of Alizarin.—In the pure state alizarin crystallises in beautiful red prisms or needles melting at 289°. It is readily soluble in alcohol and ether, but only dissolves sparingly in water, even when heated. Alkalis dissolve it with production of a deep violet red solution. Alizarin yields insoluble coloured "lakes" with mordants; with aluminium and tin oxides the colour is red, with chromium oxide a brownish violet and with ferric oxide a violet black.[1] It is by the aid of these mordants that the alizarin is attached to the fabric, and the lakes, of which aluminium red is the most important, therefore constitute the actual dye-stuffs.

Alizarin and the closely related compounds purpurin, anthrapurpurin and flavopurpurin are typical mordant dyes. They dye both wool and cotton with the aid of mordants, giving colours which are very fast to light and washing. Consequently they are of great value commercially.

Turkey Red Process

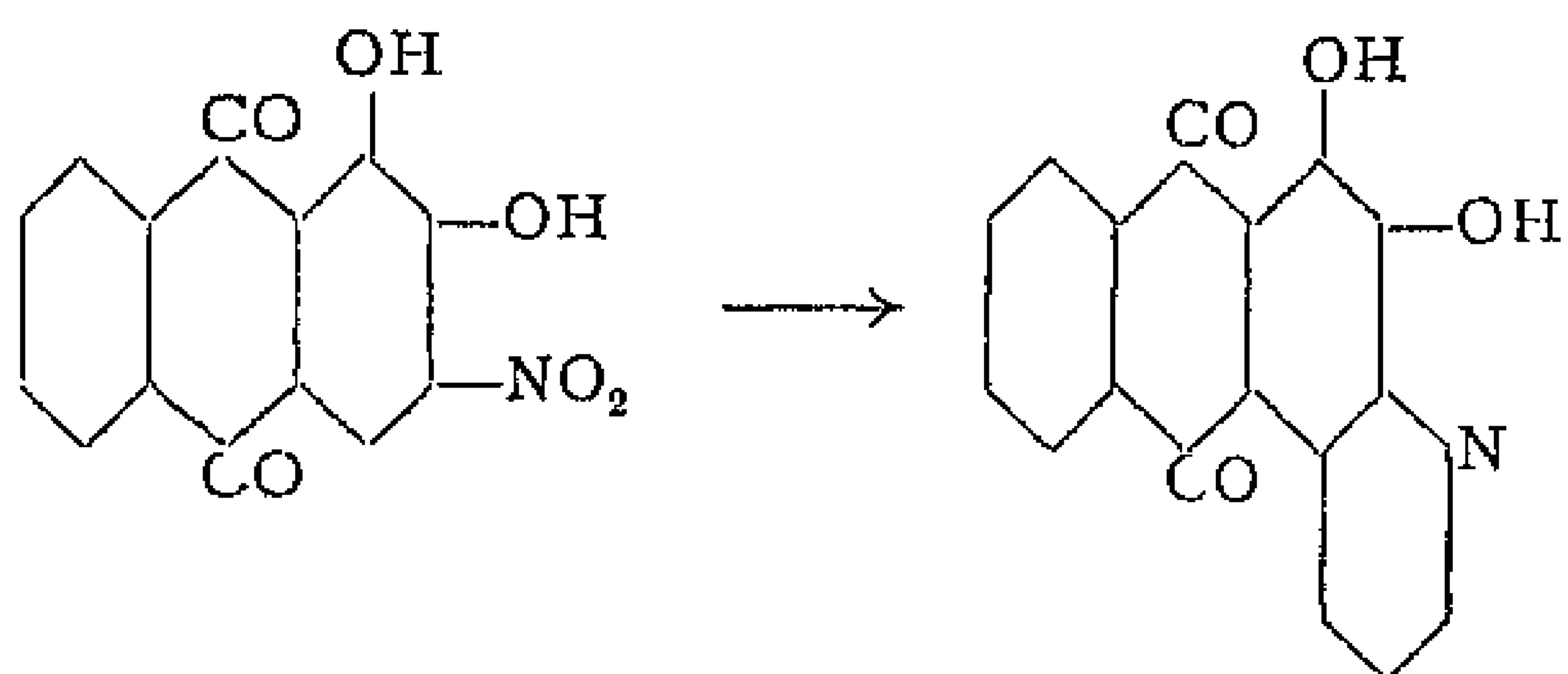
In this process the cotton fabric or yarn to be dyed is steeped in an aqueous solution of Turkey Red oil[2] and dried. It is then mordanted with aluminium acetate, dried, and dyed in an alizarin bath containing Turkey Red oil and a little chalk. Finally, the material is steamed under pressure and the colour cleared by washing with soap. In this manner there is obtained the fiery Turkey Red, which is very fast to washing, acids and light, and contains a complex colour lake probably composed of alizarin, hydroxy-oleic acid, alumina and lime.

When brominated in glacial acetic acid solution alizarin readily yields 3-*bromo-alizarin*, m.p. 260° to 261°; with bromine water 3-*bromo-alizarin quinone* is obtained.[3]

Alizarin gives valuable products on nitration. The resulting *nitro-alizarin*, $C_{14}H_7(NO_2)O_4$, is mainly the β-compound, and is used under the

[1] For alizarin iron lakes, see A. W. Bull and J. R. Adams, *J. Phys. Chem.*, 1922, 26, 660.
[2] **Turkey Red oil** is prepared from castor oil, which contains glycerides of unsaturated fatty acids and of hydroxy-oleic acid, $C_{17}H_{32}(OH).COOH$. Concentrated sulphuric acid is dropped gradually, with stirring, into cooled castor oil, when the latter is hydrolysed and the sulphuric acid partly adds on to the double bonds of the resulting unsaturated acids, and partly esterifies the hydroxy-acid to give a ricinoleic sulphuric acid, $C_{17}H_{32}\begin{cases} O.SO_2OH \\ COOH \end{cases}$. After washing with a solution of sodium sulphate or common salt, the product is neutralised with ammonia, and the liquid, which is then readily soluble in water, is placed on the market as Turkey Red oil.
[3] O. Dimroth, Schultze and Heinze, *Ber.*, 1921, 54, 3035.

name of **alizarin orange** With alumina as mordant it dyes an orange colour When heated with glycerol and sulphuric acid (*cf* quinoline synthesis) it yields **alizarin blue**, which may be used as a substitute



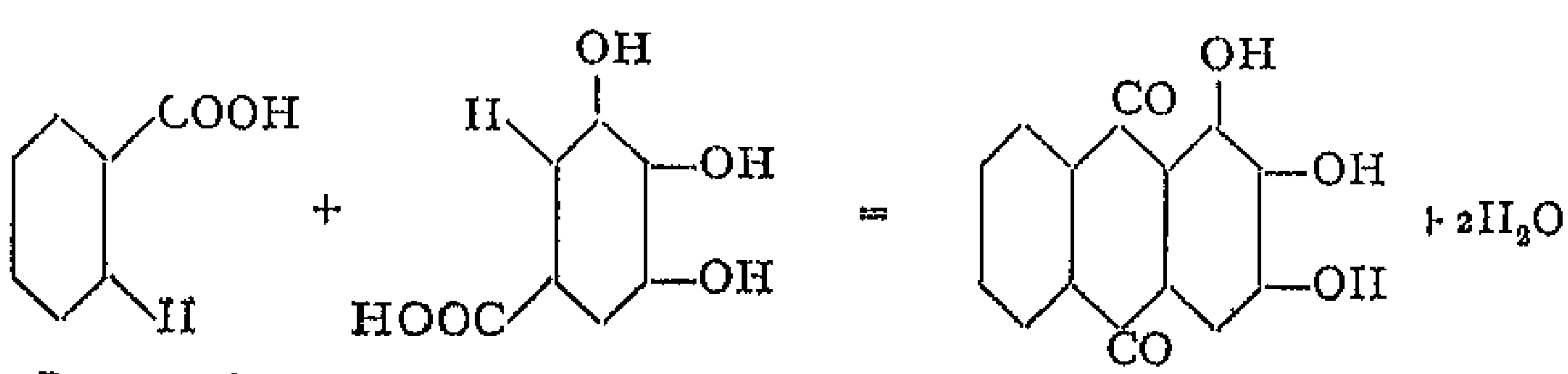
Nitro alizarin   Alizarin blue

for indigo blue in wool and cotton dyeing Alizarin blue bears the same structural relationship to alizarin as quinoline does to benzene It is employed in the form of its water-soluble sodium bisulphite compound, which is the *alizarin blue S* of commerce

Trihydroxy-anthraquinones, $C_{14}H_5O_2(OH)_3$

Some of these compounds are also valuable mordant dyes

Anthragallol, 1 2 3-*trihydroxy-anthraquinone*, is prepared by heating equimolecular amounts of benzoic acid and gallic acid with concentrated sulphuric acid



Benzoic acid   Gallic acid   Anthragallol

It forms brown lakes with chromium mordants and is used under the name of "alizarin brown" or "anthracene brown"

Purpurin, 1 2 4-*trihydroxy anthraquinone*, as already stated, is found with alizarin in madder root, and can be obtained by oxidising alizarin with manganese dioxide and sulphuric acid It is very little used **Flavopurpurin,** 1 2 6- and **iso-** or **anthra-purpurin,** 1 2 7-trihydroxy-anthraquinones are produced by fusing anthraquinone disulphonates with sodium hydroxide and potassium chlorate The former gives a scarlet red with aluminium mordant, and the latter a yellower shade of red They are employed chiefly in cotton printing

Polyhydroxy-anthraquinones

Polyhydroxy-anthraquinones, which are also of technical interest, may be obtained from anthraquinone or the above hydroxy derivatives by oxidation with sulphuric acid (see p 540 *et seq*)

Alizarin Bordeaux, 1 2 5 8 *tetrahydroxy-anthraquinone*, is formed by heating alizarin with fuming sulphuric acid With a chromium mordant it yields a lake of purple tint **Alizarin cyanine,** 1 2 4 5 8-pentahydroxy-anthraquinone, $C_{14}H_3O_2(OH)_5$ is obtained by oxidising alizarin bordeaux with manganese dioxide and sulphuric acid It gives a purple shade of blue with chromium mordant **Rufigallic acid,** 1 2 3 5 6 7-*hexahydroxy-anthraquinone*, is produced from gallic acid by heating with concentrated sulphuric acid, when 2 mols of the gallic acid condense with one another (*cf* anthragallol) It colours a chromium-mordanted fabric brown **Anthracene blue,** a position isomeride of rufigallic acid, is obtained by heating dinitro-anthraquinone with fuming sulphuric acid It forms a pure blue chromium lake

It should be noted that a large number of sulphonic derivatives of the above dyes are also used in the form of their soluble sodium salts, under the name of "alizarin acid dyes," for dyeing woollen goods Amino-hydroxy-anthraquinones and amino anthraquinones, which cannot be described here, are also largely employed as dye-stuffs[1]

Influence of Ortho hydroxylation on the Nature of Hydroxy-anthraquinone Dyes—It has already been emphasised that the formation of insoluble lakes with metallic mordants is of the highest importance for the practical utilisation of hydroxy-anthraquinones in wool dyeing and cotton printing

Liebermann and Kostanecki have shown that the presence of one hydroxyl group in the above compounds does not confer the property of forming coloured lakes in sufficiently high degree to give a good dye For this purpose it is necessary to have two hydroxyl groups which must stand in the ortho- or "alizarin" position to one another[2] Other positions of the hydroxyls either fail to give strong dyeing properties or lead only to improvement with respect to a few special mordants

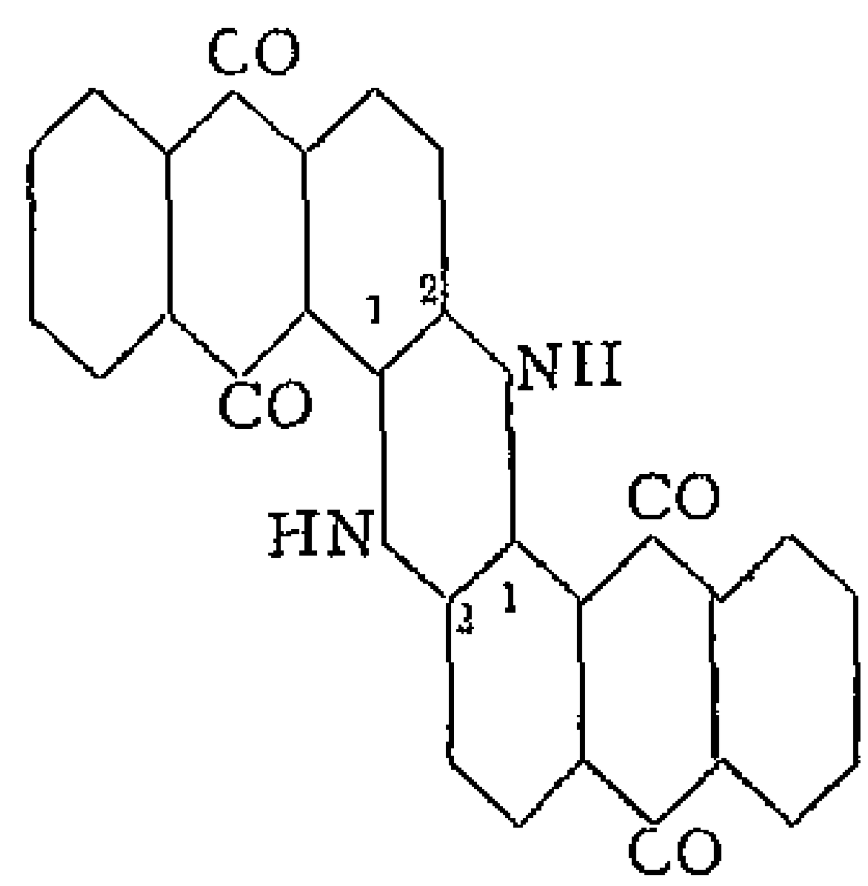
It must therefore be assumed that, in the formation of coloured salts of the type of lakes, two hydroxyl groups in adjacent positions are capable of exerting an influence not attained by hydroxyl groups in other positions

Werner[3] has developed a general theory of mordant dyes, according to which the power of a chemical compound to yield coloured lakes with mordants depends on the formation of inner complex salts

[1] See Cain and Thorpe, *The Synthetic Dye stuffs* (Griffin, 1913) [2] *Ann*, 240, 245 *Ber*, 1887, 20, 3146, 1889, 22, 1347, 1893, 26, 1574, 1901, 34, 1562, 2344, 1902, 35, 1497 *Cf* also Georgievics, *Monats*, 1911, 32, 329 [3] A Werner, *Ber*, 1908, 41, 1062

From this point of view mordant dyes contain a salt-forming group and a group capable of producing a co-ordinative linking with the metallic atom, in such relative positions that an inner metallic complex salt may result

Indanthrene, *N-dihydro-1 2 2′ 1′-anthraquinone-azine* When β-amino-anthraquinone is fused with potassium hydroxide at 200° to 300°, the potassium salt of a blue hydro-compound is obtained, which on being dissolved in water in the presence of air deposits the blue dye indanthrene This dye-stuff is remarkable for the beauty and permanence of the blue shades it produces From its mode of formation and general behaviour it is assigned the following constitution,[1] according to which it is regarded as a derivative of dihydro-phenazine (described later)



Indanthrene

Indanthrene is exceedingly stable Owing to its insolubility it cannot be attached directly to the fibre, but with alkaline hydrosulphite solution it yields a blue reduction product, which is soluble in alkali and extremely sensitive towards atmospheric oxygen In this form it is brought on to the fabric It resembles indigo in being a blue *vat dye* (p 601), and is the first genuine vat dye of the anthracene series The bath, however, is so strongly alkaline that it cannot be used for dyeing wool, but only for cotton A number of halogen substitution products and other derivatives of indanthrene (*e g*, algol blue 3 G, algol green G) are also used extensively as vat dyes

By conducting the fusion of β-amino-anthraquinone with alkali at the very high temperature of 330° to 350°, dissolving the melt in water in the presence of air and filtering off the alkali-soluble by-products of the reaction, there is formed in place of indanthrene a yellow dye stuff known as **flavanthrene**[2] or **indanthrene yellow G** The technical method of preparation is to treat β amino-anthraquinone with antimony pentachloride in boiling nitrobenzene solution Indanthrene

[1] R Scholl, *Ber*, 1903, 36, 3410, 3427. See also *Ber*, 1911, 44, 1727 [2] R Scholl, *Ber*, 1907, 40, 1691

and flavanthrene are also produced together in variable proportions when β-amino-anthraquinone is treated with acid oxidising agents, such as chromic acid or manganese dioxide and sulphuric acid

Another substance which appears to be related to anthracene is aloin, $C_{16}H_{16}O_7$(?), a strong purgative present in aloes, the dried juice of various species of aloe On heating with zinc dust it yields anthracene, and when oxidised with sodium peroxide gives **emodin**, a 1 6 8 trihydroxy 3 methyl anthraquinone[1] With mono per sulphuric acid a tetrahydroxy methyl anthraquinone is formed

XVI

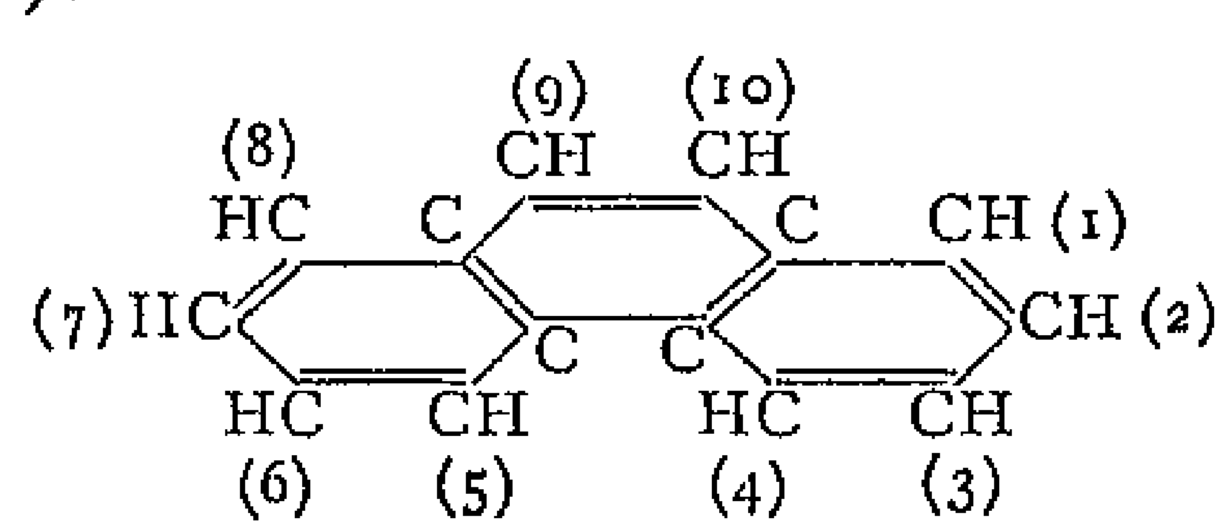
Phenanthrene Group

Phenanthrene, as already stated on p 534, is found with its structural isomeride anthracene in the anthracene oil of coal tar After purification of the crude anthracene by means of pyridine bases or solvent naphtha, the phenanthrene, owing to its greater solubility, remains in the mother liquors, from which it is isolated The two hydrocarbons may also be separated by the use of carbon disulphide, or by partial oxidation, which results in anthracene being first attacked In any case the production of phenanthrene is a matter of small technical importance, since all efforts to make use of it in the dye-stuff industry have so far been fruitless

In the pure state phenanthrene forms white glistening plates, m p 99° and b p 340° It dissolves very easily in ether and benzene, but less readily in alcohol, glacial acetic acid and carbon disulphide The solutions exhibit a blue fluorescence

Constitution and Synthesis of Phenanthrene

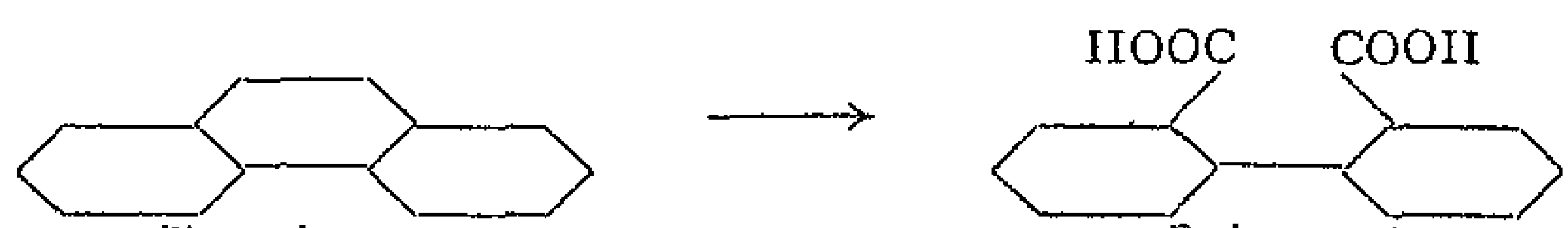
From its chemical behaviour and methods of synthesis, phenanthrene has been assigned the following constitution (Fittig and Ostermayer, Gräbe and Glaser):



[1] *Arch d Pharm*, 1911, 249, 311, 445 *J pr Ch*, [2], 1911, 83, 211 *Helv Chim Acta*, 1925, 8, 26, 140

The positions occupied by substituents in phenanthrene derivatives are indicated by the use of numbers as shown above.

As will be seen from the formula, phenanthrene may be regarded either as a derivative of diphenyl or of naphthalene. Its connection with diphenyl is shown by a number of syntheses, as well as by its degradation to this hydrocarbon. For example, when phenanthrene is oxidised with chromic acid it first yields phenanthraquinone (see p. 555) and then diphenic acid (p. 489), a derivative of diphenyl. Hence it must be derived from diphenyl, $C_6H_5 \cdot C_6H_5$, in such a way that the group C_2H_2 is attached to each benzene nucleus in an *o*-position to the bond linking the nuclei.



Phenanthrene Diphenic acid

The conversion of phenanthraquinone and its derivatives into derivatives of diphenyl-methane or fluorene, as described on p. 493, also supports this deduction. Further confirmation is obtained from syntheses.

Phenanthrene may be synthesised by the following methods:

1. By various pyrogenic reactions, such as by leading stilbene, dibenzyl, toluene, *o*-ditolyl, or a mixture of diphenyl and ethylene through red-hot tubes.

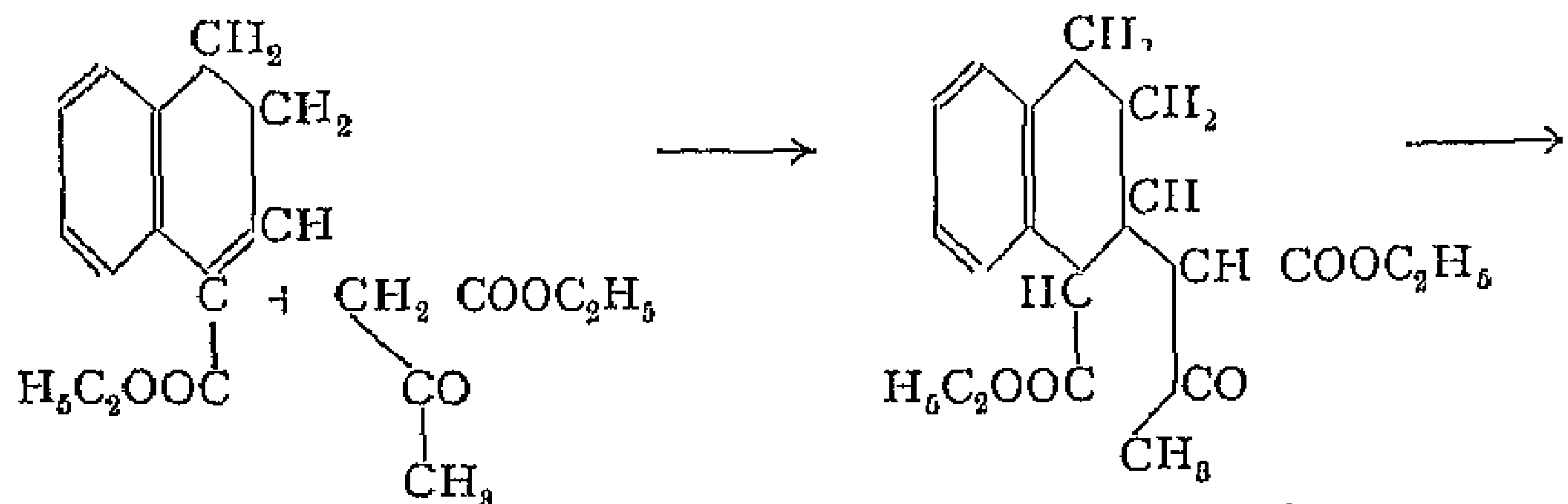
$$\begin{array}{c} C_6H_4 \cdot CH_3 \\ | \\ C_6H_4 \cdot CH_3 \\ \textit{o-Ditolyl} \end{array} \xrightarrow{\text{Heat}} \begin{array}{c} C_6H_4—CH \\ | \qquad \| \\ C_6H_4—CH \\ \text{Phenanthrene} \end{array} \xleftarrow{\text{Na}} \begin{array}{c} Br \cdot C_6H_4 \cdot CH_2Br \\ \\ Br \cdot C_6H_4 \cdot CH_2Br \\ \textit{o-Bromobenzyl bromide} \end{array}$$

2. By treating *o*-bromobenzyl bromide with sodium.

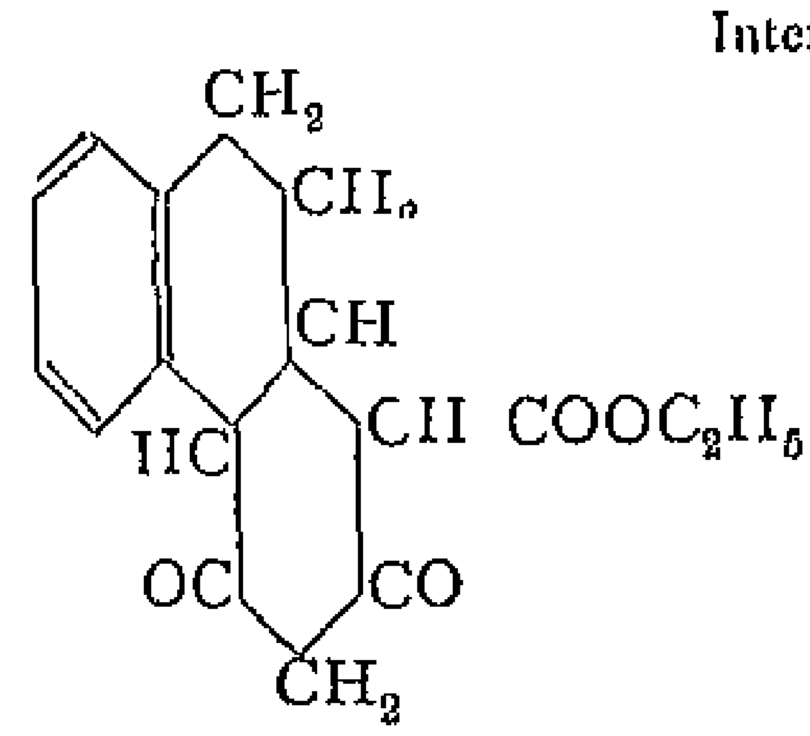
3. From coumarone by heating with benzene.

$$\begin{array}{c} C_6H_4—CH \\ | \qquad \| \\ O——CH \\ \text{Coumarone} \end{array} + C_6H_6 = \begin{array}{c} C_6H_4—CH \\ | \qquad \| \\ C_6H_4—CH \end{array} + H_2O$$

4. The relationship between phenanthrene and naphthalene is illustrated by the following synthesis from a derivative of naphthalene: Dihydro-α-naphthoic ester (I.) condenses with acetoacetic ester to give a diketo-octahydro-phenanthrene carboxylic ester (II.), which on hydrolysis and elimination of carbon dioxide yields diketo-octahydro-phenanthrene. The latter on distillation with zinc dust is converted into phenanthrene.

I 

Intermediate product

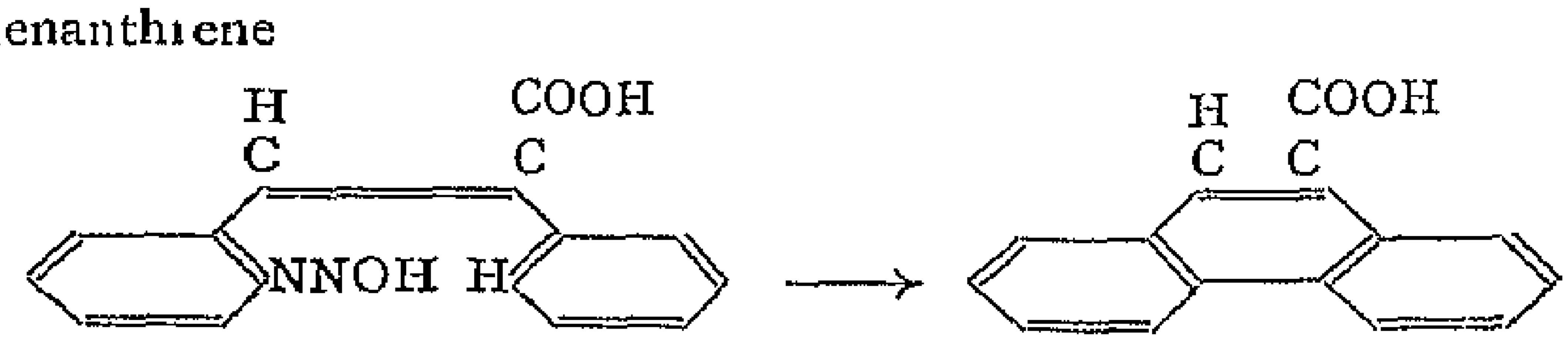
II 

5 A general method, developed by Pschorr[1] for preparing phenanthrene and its derivatives without employing high temperatures, is based on Perkin's reaction (p 441)

o Nitrobenzaldehyde may be condensed with the sodium salt of phenylacetic acid, in the presence of acetic anhydride, to form α-phenyl-*o*-nitrocinnamic acid

$$NO_2\ C_6H_4\ CHO + HOOC\ CH_2\ C_6H_5 = NO_2\ C_6H_4\ CH\ C\!\begin{cases} COOH \\ C_6H_5 \end{cases} + H_2O$$

This may be reduced to the amino-compound, which when diazotised and shaken in sulphuric acid solution with copper powder, yields nitrogen, water and phenanthrene-10-carboxylic acid The latter loses carbon dioxide on distillation and is converted into phenanthrene



This procedure is adapted to the preparation of a large number of phenanthrene derivatives, since in place of nitrobenzaldehyde and phenyl acetic acid we may also employ their substitution products As will be seen shortly, the method has been used for the preparation of certain phenanthrene derivatives which are of special interest ing hydrolytic products of alkaloids In addition, this synthesis furnished valuable information regarding the constitution of a

[1] R Pschorr, *Ber*, 1896, 29, 496

number of mono-substitution products of phenanthrene, such as sulphonic acids, amino- and nitro-compounds.

Windaus[1] has recently introduced a small modification of Pschorr's synthesis. Whereas Pschorr utilises the condensation product of *o*-nitro-aldehydes and phenylacetic derivatives, Windaus employs the products obtained from the unsubstituted aldehydes and oxindole (p. 589). In the former case the nitrogen required for ring closure is present in the aromatic aldehyde; in the latter it is contained in the phenylacetic derivative (oxindole). Windaus was thus enabled to synthesise phenanthrene derivatives (*e.g.* 9-methyl-phenanthrene, m.p. 88° to 89°) which he had isolated as degradation products of the alkaloid colchicin.

6. Diphenyl-*o*.*o*′-dialdehyde, when warmed with an aqueous alcoholic solution of potassium cyanide, undergoes a form of benzoin condensation and is converted into phenanthraquinone.[2]

$$\begin{array}{l} C_6H_4\cdot CHO \\ | \\ C_6H_4\cdot CHO \end{array} \longrightarrow \begin{array}{l} C_6H_4\text{—}CO \\ |\qquad\quad | \\ C_6H_4\text{—}CO \end{array}$$

7. Benzil yields phenanthraquinone when melted with aluminium chloride. This synthesis may also be applied to derivatives of benzil.[3]

$$\begin{array}{l} C_6H_5\text{—}CO \\ \qquad\quad | \\ C_6H_5\text{—}CO \end{array} \xrightarrow{-2H} \begin{array}{l} C_6H_4\text{—}CO \\ |\qquad\quad | \\ C_6H_4\text{—}CO \end{array}$$

Chemical Behaviour of Phenanthrene.—In its chemical reactions phenanthrene is more closely related to diphenyl than to naphthalene. The central benzene ring, formed by linking up the diphenyl rings with the group CH : CH, is less stable than the other two. In other words, the (9 : 10) "bridge" of phenanthrene is attacked by reagents much more easily than the rest of the molecule and is also readily ruptured with the formation of diphenyl derivatives (see p. 547).

Two examples will illustrate the ease with which the bridge is attacked. Bromine reacts with phenanthrene to give the 9 : 10-dibromide, and this on being warmed splits off hydrogen bromide and is transformed into 9-bromo-phenanthrene.

$$\underset{\text{Phenanthrene}}{\begin{array}{l} C_6H_4\text{—}CH \\ |\qquad\quad \| \\ C_6H_4\text{—}CH \end{array}} \xrightarrow{Br} \underset{\substack{\text{Phenanthrene} \\ \text{dibromide}}}{\begin{array}{l} C_6H_4\text{—}CHBr \\ |\qquad\quad | \\ C_6H_4\text{—}CHBr \end{array}} \xrightarrow{-HBr} \underset{\substack{\text{9-Bromo-} \\ \text{phenanthrene}}}{\begin{array}{l} C_6H_4\text{—}CH \\ |\qquad\quad \| \\ C_6H_4\text{—}CBr \end{array}}$$

In the presence of platinum black, hydrogen unites with phenanthrene to form 9 : 10-dihydro-phenanthrene,[4] $C_{14}H_{12}$, a white crystalline mass of melting-point 94° to 95°.

[1] A. Windaus and co-workers, *Ber.*, 1924, 57, 1871, 1875. [2] F. Mayer, *Ber.*, 1912, 46, 1102. [3] R. Scholl and Schwarzer, *Ber.*, 1922, 55, 324. [4] J. Schmidt and F. Fischer, *Ber.*, 1908, 41, 4225. See also *Ber.*, 1907, 40, 4240.

Phenanthrene also possesses many points in common with its structural isomeride anthracene, from which it differs, however, not only in its greater solubility in the common solvents, but above all in the fact that it is less readily affected by oxidising agents

Substitution Products of Phenanthrene

From the established formula of phenanthrene may be derived five different monosubstitution products, corresponding to the positions 1, 2, 3, 4, and 10 respectively

It will readily be seen that the hydrogen atoms in the "bridge" are similarly situated, hence the 9- and 10 substitution products are the same

A comparatively large number of disubstitution derivatives is theoretically possible, and with still further substitution the number of isomerides increases in a manner alarming to the experimenter

This enormous increase in the possibilities of isomerism presents great difficulties in the way of preparing phenanthrene derivatives directly from the hydrocarbon according to methods usual in the aromatic series In addition, the physical properties of many phenanthrene compounds are not favourable to experimental investigation

For these reasons and more particularly owing to the fact that, contrary to expectation, it has not been possible to use these compounds on any considerable scale in the dyeing industry, chemists for decades back have hesitated to enter upon a systematic study of the phenanthrene group Only in recent years have attempts been made from different quarters to supply the deficiency An impetus towards this end was given by researches proving the existence of a close relationship between phenanthrene and certain important plant alkaloids

As the result of the work of a number of different investigators,[1] it has been established with certainty that *morphine*, *codeine* and *thebaine* contain a phenanthrene nucleus, and further that morphine and codeine are derived from a *tetrahydro-phenanthrene*, and thebaine from a *dihydro-phenanthrene*

The Corydalis alkaloids and colchicin also contain the phenanthrene structure, and in certain sesquiterpenes a hydrogenated phenanthrene or anthracene nucleus may be present[2]

Following the above discoveries a number of investigations were made with the object of preparing new derivatives of phenanthrene, either synthetically or directly from the hydrocarbon[3]

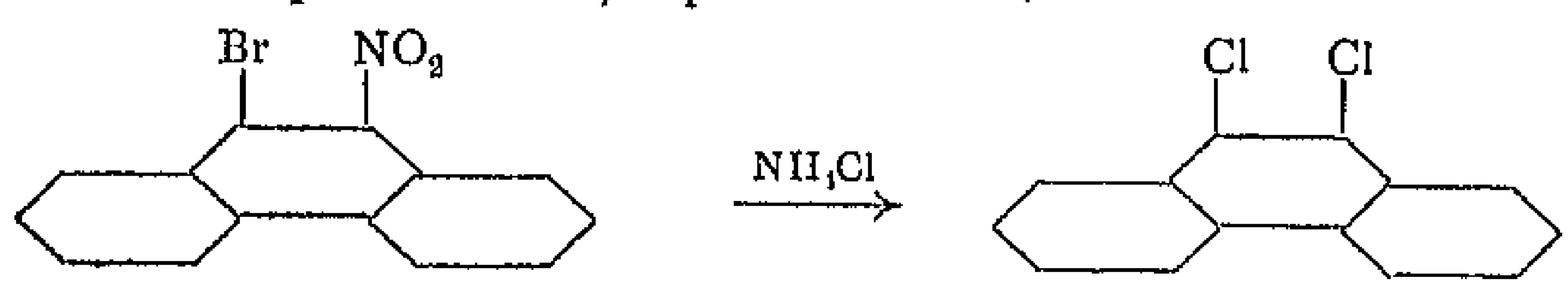
Thus, for example, *3-nitro-phenanthrene*, m p 170° to 171°, and *9-nitro-phenanthrene*, m p 116° to 117°, have been prepared by direct

[1] Vongerichten, *Ber*, 1901, 34, 767, 1162, 2722 Knorr, *Ber*, 1894, 27, 1146 Freund, *Ber*, 1899, 32, 168 [2] F W Semmler, *Ber*, 1907, 40, 3521, also *J C S Ann Rep*, 1924, p 101 [3] A Werner and co workers, *Ann*, 1902, 321, 248, 322, 135 J Schmidt and co-workers, *Ber*, Vols 33 60 H Sandqvist, *Ann*, 1913, 398, 125, 1918, 417, 1

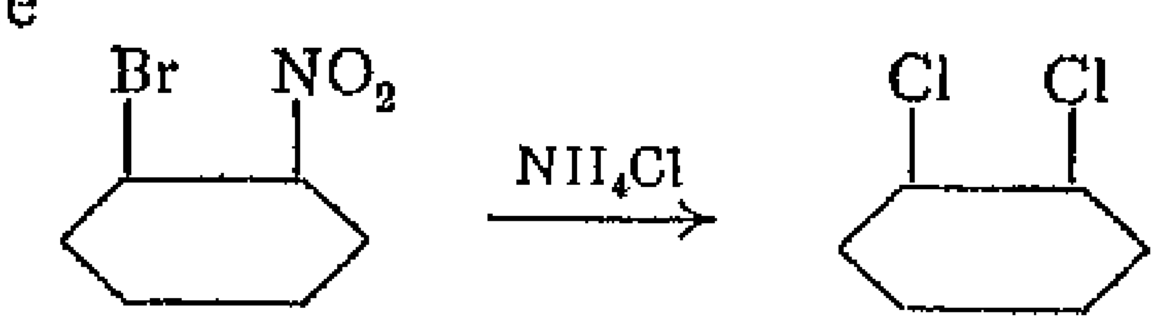
nitration, and from these the corresponding *amino-phenanthrenes* have been obtained by reduction.

Nevertheless the preparation of nitro-phenanthrenes by direct nitration is tedious, owing to the resinification which so easily occurs. Halogen-substitution products of phenanthrene are less troublesome to nitrate, and when the 9-bromo-phenanthrene described on p. 549 is heated with nitric acid it yields 9-*bromo*-10-*nitro-phenanthrene*, m.p. 206°.

An observation of general interest has been made in connection with this compound.[1] When heated in a closed tube to 320° with ammonium chloride, it is converted comparatively smoothly into 9:10-*dichloro-phenanthrene*, m.p. 160° to 161°.



The reaction may also be applied to other aromatic compounds. For example, *o*-bromo-nitrobenzene under the same conditions yields *o*-dichloro-benzene.



A condition for the success of this reaction is the *o*-position of the substituents, since *m*- and *p*-bromo-nitrobenzenes remain unchanged.

Sulphonation of phenanthrene leads to the production of 3-, 2- and 9-*phenanthrene sulphonic acids*, $C_{14}H_9 \cdot SO_3H$.

Hydroxy-phenanthrenes

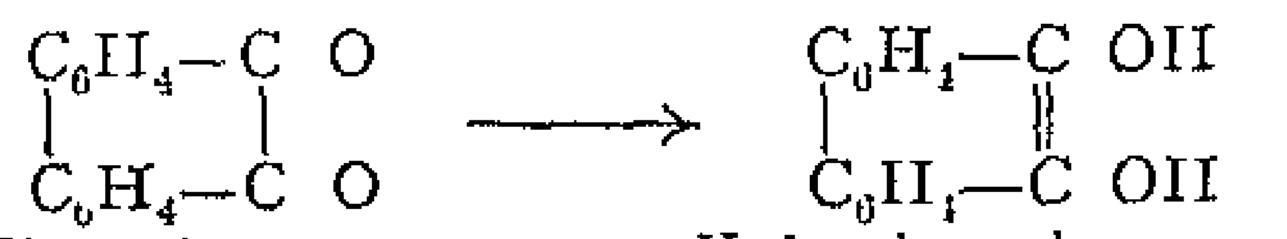
Of more importance than the compounds just described are the **hydroxy-phenanthrenes**, certain of which, as will be seen later, have been obtained as degradation products of the opium alkaloids morphine, codeine and thebaine. They are therefore of interest in connection with the constitution of these substances. Hydroxy-phenanthrenes may be prepared from the sulphonic acids by fusion with potash, from the amino-derivatives by way of the diazo-reaction, or by the synthetic method of Pschorr (p. 548).

All of the five possible **monohydroxy-phenanthrenes** are known, either in the free state or as the methyl ethers.

1-*Hydroxy-phenanthrene*,[2]	melting point	156°,	*Methyl ether*,	melting point	106°
2-*Hydroxy-phenanthrene*,	"	168°,	"	"	99°
3-*Hydroxy-phenanthrene*,	"	124°,	"	"	63°
4-*Hydroxy-phenanthrene*,	"	106° to 109°,	"	"	68°
9-*Hydroxy-phenanthrene*,	"	153			

[1] J. Schmidt and Ladner, *Ber.*, 1904, 37, 4402; J. Schmidt and Wagner, *Ann.*, 1912, 387, 164. [2] J. B. Shoesmith and Guthrie, *J.C.S.*, 1928, 2332.

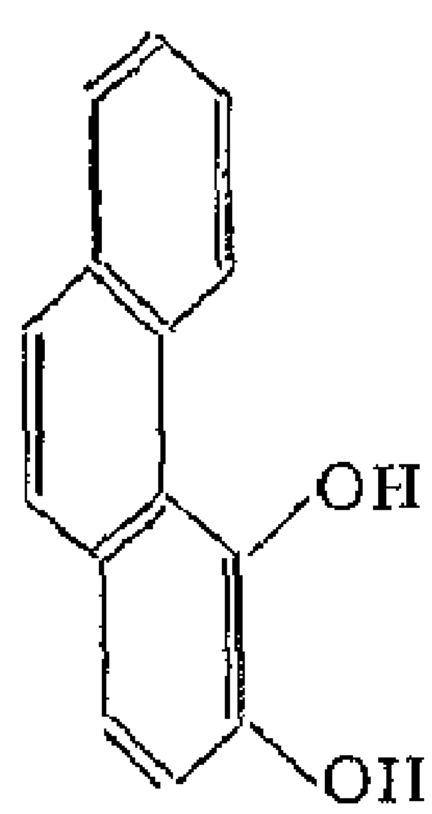
Among the **dihydroxy-derivatives**, the most accessible is 9 10-*dihydroxy-phenanthrene* or hydro-phenanthraquinone, m p 147° to 148° It is conveniently prepared by reducing phenanthraquinone with hydrogen sulphide, or with the calculated amount (1 mol) of phenyl hydrazine in alcoholic solution



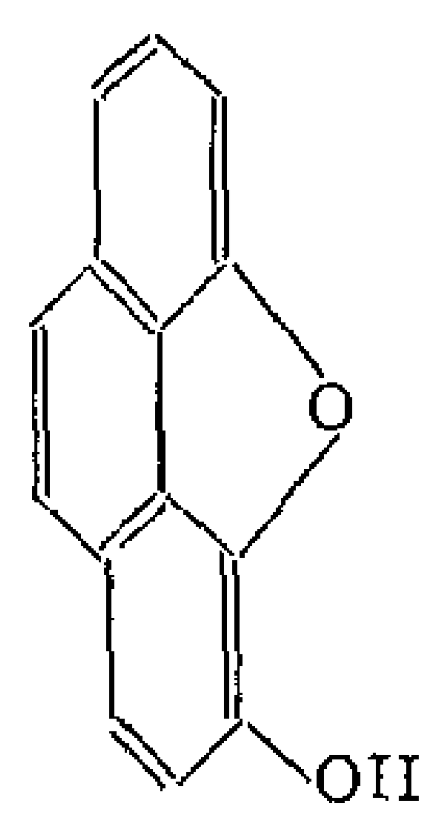
Phenanthraquinone — Hydro phenanthraquinone

In a similar manner the nitro-derivatives of phenanthraquinone may be converted into the corresponding hydro-phenanthraquinones[1]

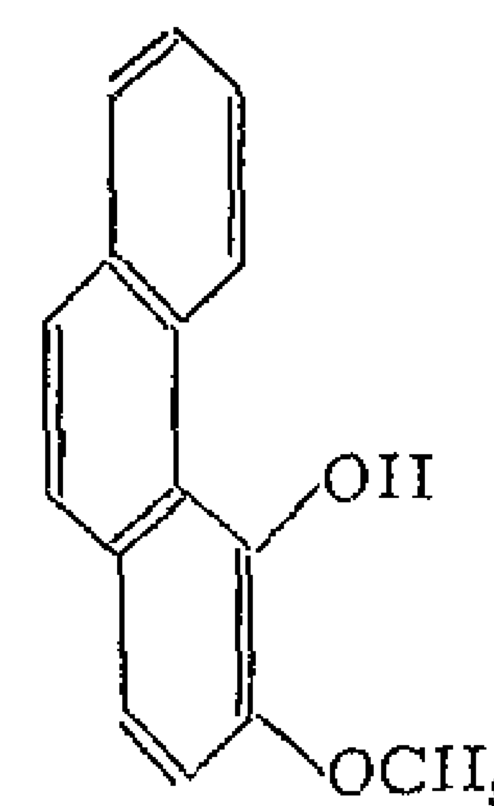
The compounds *morphol* and *morphenol* are important degradation products of morphine and its methyl ether codeine



Morphol, 3 : 4 dihydroxy-phenanthrene, m p 143°



Morphenol, m p 135°



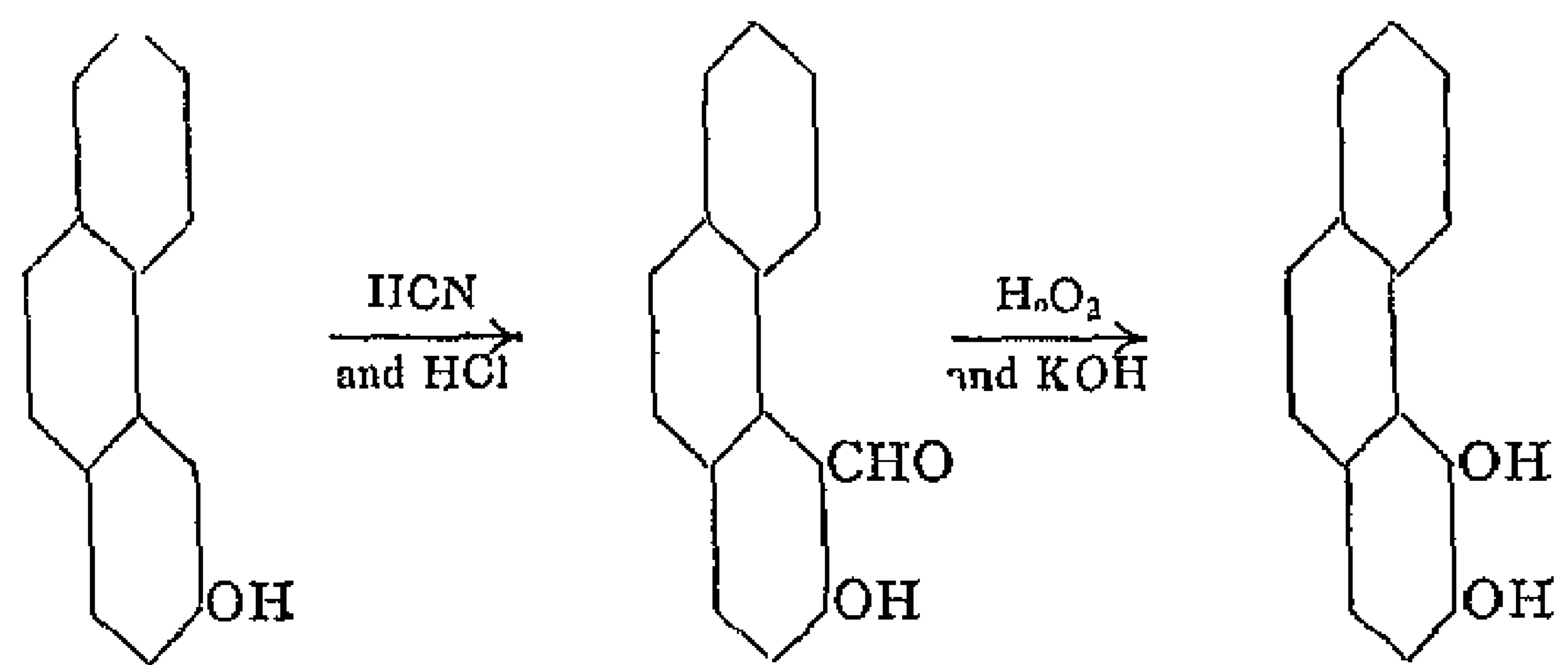
Methyl morphol, 3-methoxy 4-hydroxy phenanthrene

Morphol is a disruption product of morphine in which no nitrogen is present It was prepared from morphine methiodide by heating with acetic anhydride, and for long could only be identified generally as a dihydroxy-phenanthrene Subsequently, some information as to the position of the hydroxyl groups was obtained from the observation that the dihydroxy-phenanthraquinone prepared from morphol possessed dyeing properties[2] similar to those of alizarin, and hence should contain the hydroxyl groups in the ortho-position (see p 544) After the relationship between morphol and morphenol had been made clear by reducing the latter to the former, the structure of 3 4-dihydroxy-phenanthrene[2] was proposed for morphol Confirmation of this formula was supplied by the synthesis of dimethyl-morphol described below, and later by Barger's synthesis of morphol itself

Synthesis of Morphol[3]—This was effected from 3-phenanthrol-4-aldehyde (obtained by the interaction of 3-phenanthrol, hydrogen cyanide and hydrogen chloride in the presence of aluminium chloride) by treating it with hydrogen peroxide and potassium hydroxide in

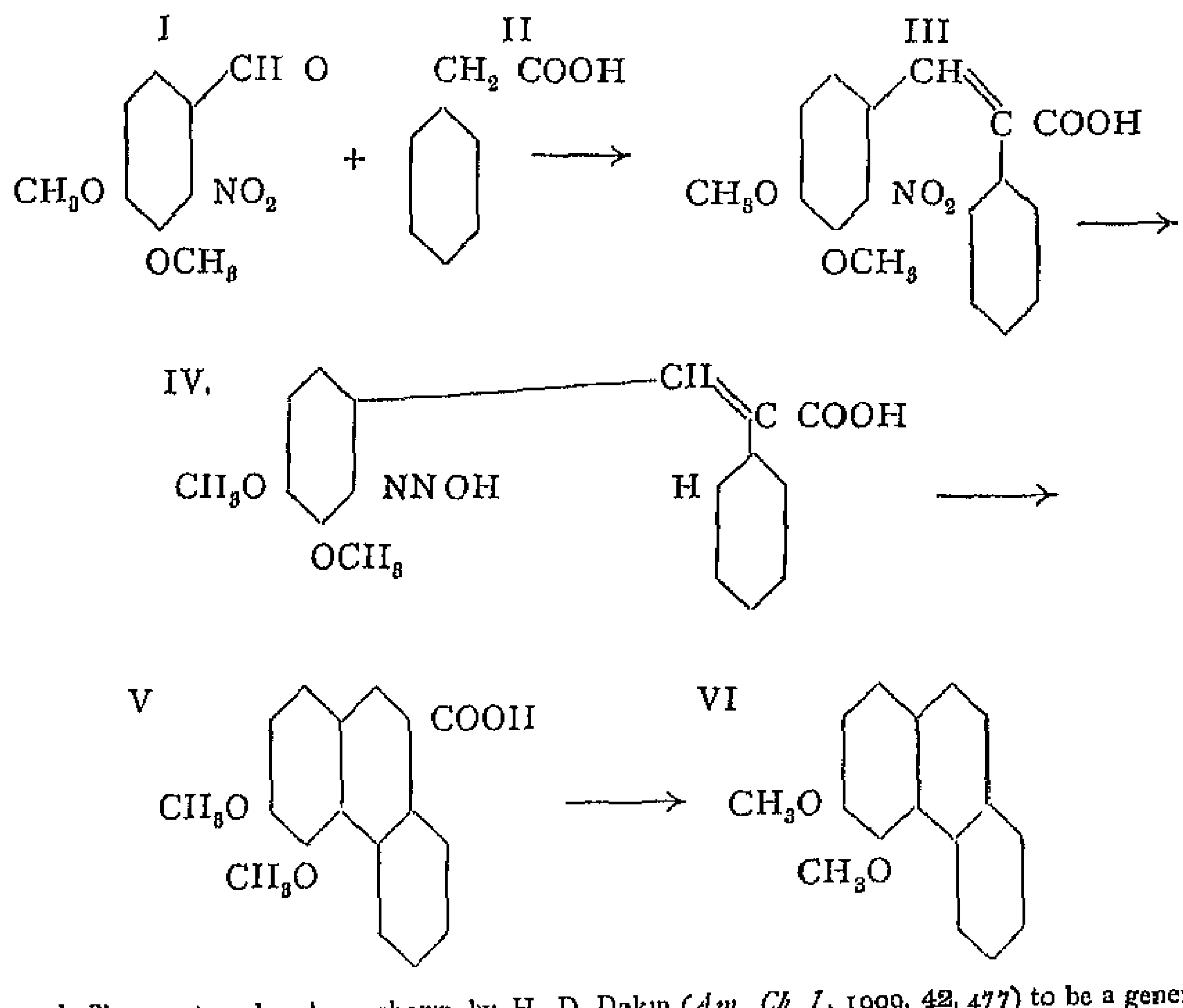
[1] J Schmidt and Kampf, *Ber*, 1902, 35, 3123 [2] Vongerichten, *Ber*, 1900, 33, 352
[3] G Barger, *J C S*, 1918, 113, 218

aqueous pyridine solution[1] The morphol or 3 4-dihydroxy-phenanthrene obtained melted at 142°



3-Phenanthrol — 3-Phenanthrol-4-aldehyde — 3 4 Dihydroxy-phenanthrene

Synthesis of Dimethyl-morphol[2]—The starting-point of this synthesis was the methyl ether of vicinal *o*-nitrovanillin (I), which was condensed with the sodium salt of phenylacetic acid (II) by Perkin's reaction to give α-phenyl-2-nitro-3 4-dimethoxy-cinnamic acid (III) The diazo-compound (IV) of the corresponding amino acid in sulphuric acid



[1] This reaction has been shown by H D Dakin (*Am Ch J*, 1909, 42, 477) to be a general method of converting hydroxy derivatives of benzaldehyde and acetophenone into polyhydric phenols [2] Pschorr and Simulcanu, *Ber*, 1900, 33, 1811

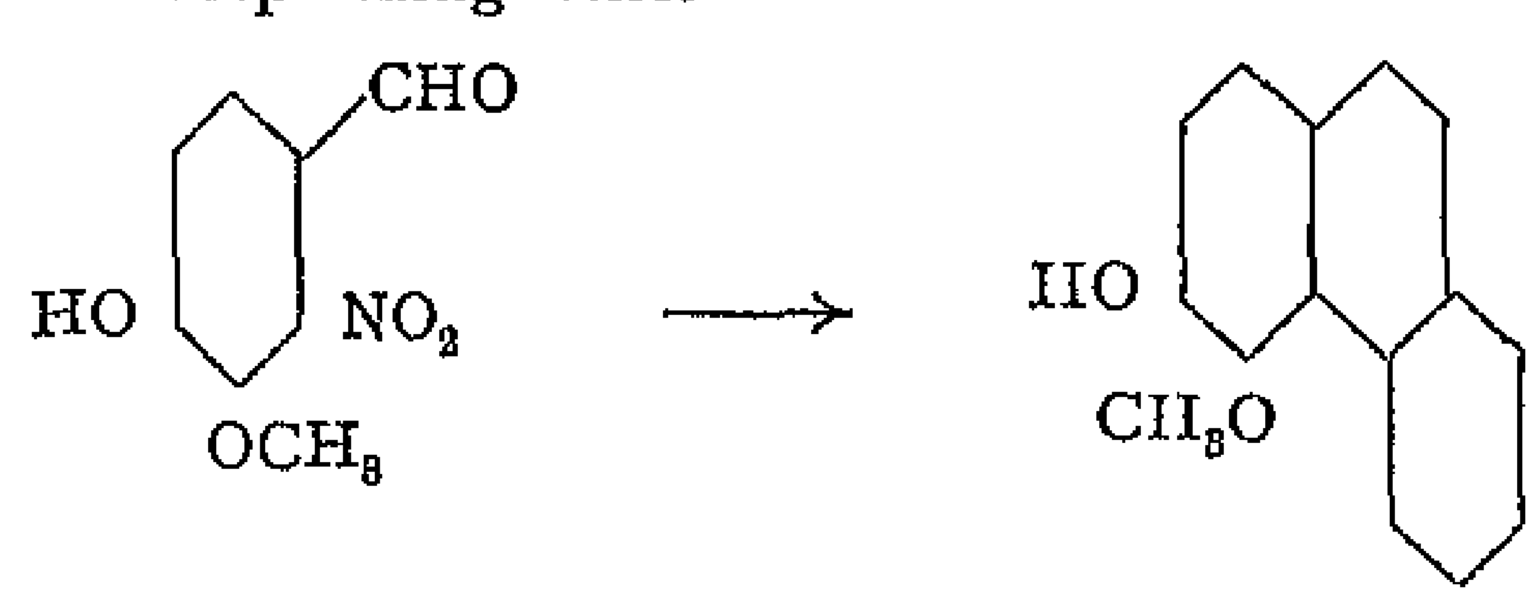
solution parted with nitrogen and water with the formation of 3 4-dimethoxy-phenanthrene-9-carboxylic acid (V), which on distillation gave carbon dioxide and dimethoxy-phenanthrene (VI)

This synthesis establishes the 3 4-positions of the two methoxyl groups, as it is improbable than any intramolecular rearrangement could take place under the above conditions of experiment

Dimethyl morphol (formula VI) crystallises from alcohol in colourless leaflets, m p 44° With picric acid it yields a double compound, m p 105° to 106°, crystallising in ruby red prisms

The synthetic 3 4-dimethoxy-phenanthrene is identical with the dimethyl-morphol prepared from methyl-morphol, a degradation product of codeine[1]

In connection with the constitution of morphine, the molecule of which contains an alcoholic hydroxyl and a phenolic group,[2] it was of importance to decide which of the hydroxyls of morphol corresponds to the phenolic hydroxyl Now codeine, a methyl ether of morphine in which the methoxy group takes the place of the phenolic hydroxyl of the latter compound, had been degraded to acetyl-methyl-morphol All that was necessary, therefore, was to determine the position of the methoxy group in this acetyl derivative The point was settled by Pschorr's synthesis of the acetyl derivative of 3-hydroxy-4-methoxy-phenanthrene by the above method, using vicinal *o*-nitrovanillin in place of the corresponding ether

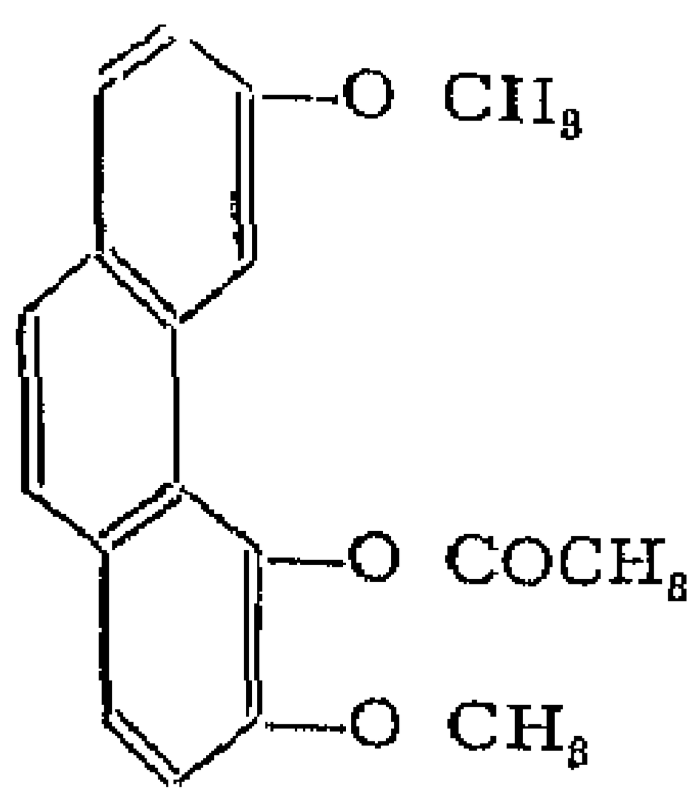


The synthetic *3-hydroxy-4-methoxy-phenanthrene* prepared in this manner differs considerably from the methyl-morphol obtained as a disruption product of α-methyl-morphimethine from codeine, hence it was concluded that the latter is represented by the structure 3-methoxy-4-hydroxy-phenanthrene This inference was shortly afterwards confirmed by the synthesis of 3-methoxy-4-acetoxy-phenanthraquinone,[3] which was found to be identical with the acetyl-methyl-morphol-quinone from morphine

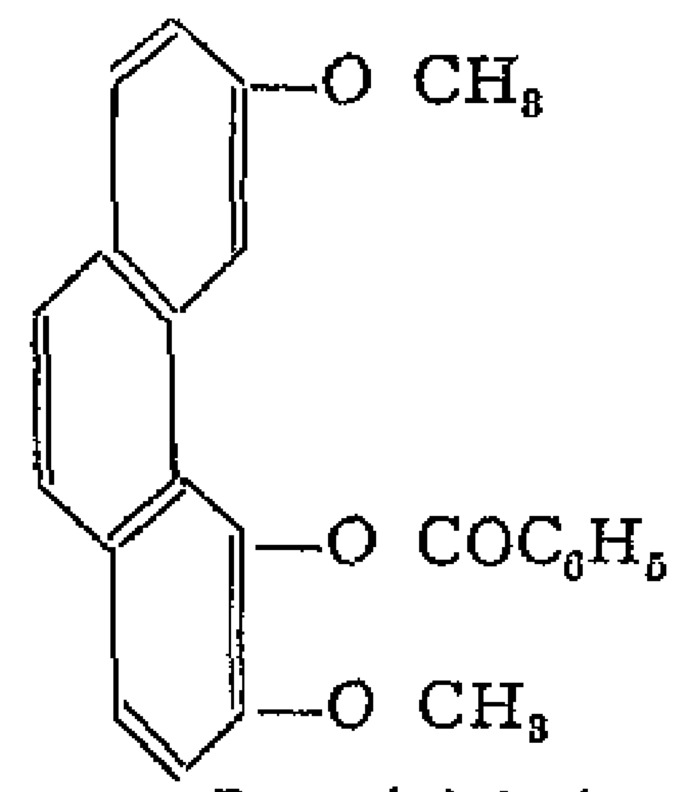
Morphenol (p 552), which represents the molecular skeleton of morphine and thebaine, yields on fusion with alkali 3 4 5-trihydroxy-phenanthrene,[4] m p 148°

[1] Vongerichten, *Ber*, 1900, 33, 1824 Hesse, *Ann*, 1884, 222, 203
[2] Matthiessen and Wright, *Proc Roy Soc*, 1869, 17, 364
[3] Pschorr and Vogtherr, *Ber*, 1902, 35, 4412
[4] Vongerichten and Dittmer, *Ber*, 1906, 39, 1718 For a synthesis of 3 4 5-*trimethoxy-phenanthrene*, see R Pschorr, *Ann*, 1912, 391, 40

e following two hydroxy derivatives of phenanthrene have been d from the opium alkaloid thebaine under different experimental ons

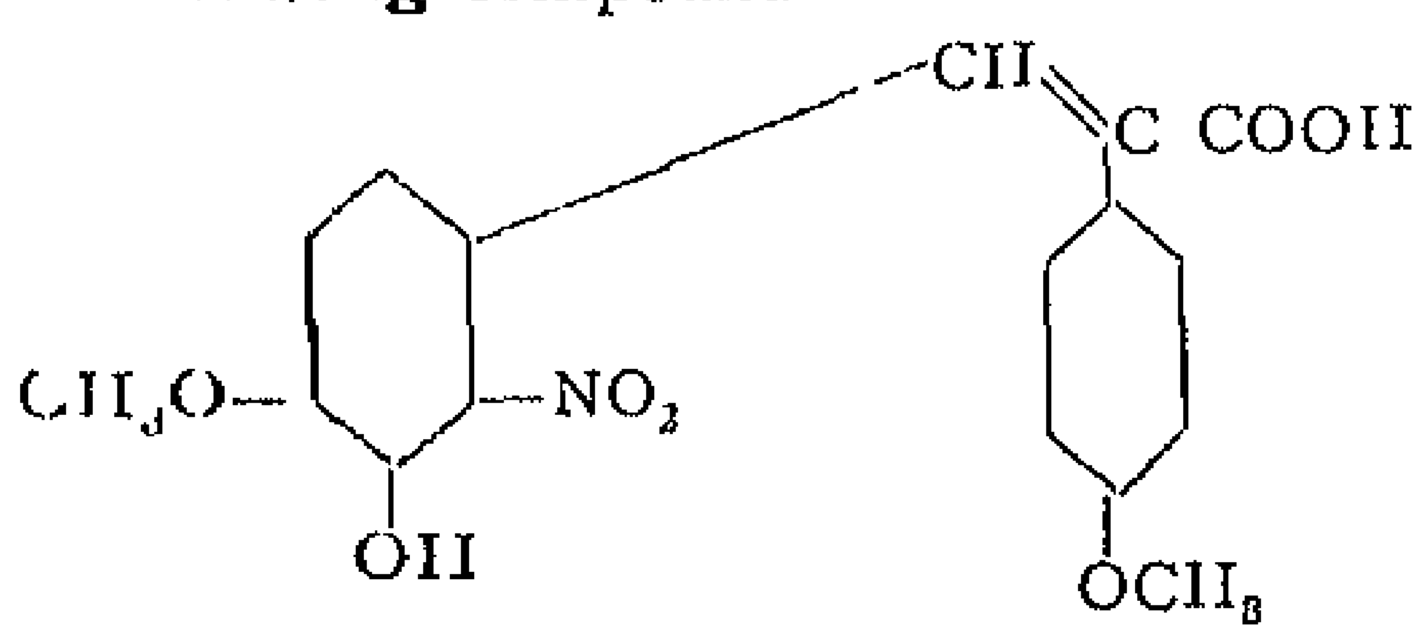


Acetyl-thebaol
(3,6 dimethoxy-4-acetoxy-phenanthrene)



Benzoyl thebaol

tyl-thebaol, m p 118° to 122°, has been prepared from thebaine ating it with acetic anhydride (Freund) When treated with ethoxide it is converted into **thebaol, 3 6 dimethoxy 4 hydroxy-nthrene,** m p 94° The constitution of thebaol was proved by r, who synthesised it from vicinal *o*-nitro-isovanillin and oxy-phenylacetic acid by the method previously described for thoxy phenanthrenes[1] The first step in the process is the ion of the following compound



s synthesis also establishes the position of the two methoxy-of thebaine, a point which will be referred to later *Benzoyl-* has been prepared in the form of colourless needles, m p 169°, action of benzoyl chloride on thebaine[2] at 0°

, 6 8 **Tetramethoxy-phenanthrene,** m p 108°, has been obtained degradation of the alkaloid morphothebaine It was also ised by Pschorr[3] by the method already quoted

Phenanthraquinone and its Derivatives

nanthraquinone, $C_{14}H_8O_2$ (formula I below), is generally d by oxidising phenanthrene with chromic acid in glacial acid solution It crystallises in orange-coloured needles,

orr, Seydel and Stohrer, *Ber*, 1902, 35, 4400 [2] Pschorr and Haas, *Ber*, 1906, 39, Pschorr and Knoffler, *Ann*, 1911, 382, 50

m p 208° At ordinary temperatures it is readily soluble in benzene but dissolves less readily in ether, alcohol and glacial acetic acid It is odourless and not volatile with steam When a solution of phenanthraquinone in glacial acetic acid is treated with sulphuric acid and toluene containing thiotolene (see p 586), a blue-green coloration is developed, after dilution with water and extraction with ether, the colour changes to violet (Laubenheimer's reaction) As already indicated under β-naphthaquinone, it is closely related to the α-diketones in its properties With hydroxylamine it forms, according to conditions, a monoxime (m p 160°) or a dioxime The former exhibits tautomerism, reacting according to either of the formulæ II*a*, or II*b*

$$\overset{\text{I}}{\begin{array}{lcl}C_6H_4 & — & C\ O\\ | & & |\\ C_6H_4 & — & C\ O\end{array}} \xrightarrow{H_2N\ OH} \overset{\text{II}a}{\begin{array}{lcl}C_6H_4 & — & C{=}N\ OH\\ | & & |\\ C_6H_4 & — & C{=}O\end{array}} \qquad \overset{\text{II}b}{\begin{array}{lcl}C_6H_4 & — & C{—}N\ O\\ | & & \|\\ C_6H_4 & — & C{—}OH\end{array}}$$

Phenanthraquinone, like other α-diketones, reacts with *o*-diamines to give phenazine derivatives Thus with *o*-phenylene diamine it condenses to form *phenanthraphenazine* (III)

$$\begin{array}{lcl}C_6H_4 & — & C\ O\\ | & & |\\ C_6H_4 & — & C\ O\end{array} + \begin{array}{l}H_2N\diagdown\\ \qquad\ \ C_6H_4\\ H_2N\diagup\end{array} = \overset{\text{III}}{\begin{array}{lcl}C_6H_4 & — & C{=}N\diagdown\\ | & & |\qquad\ C_6H_4\\ C_6H_4 & — & C{=}N\diagup\end{array}} + 2H_2O$$

The conversion of phenanthraquinone into diphenic acid by oxidation with chromic acid mixture, and the formation of diphenylene glycollic acid by heating it with aqueous potassium hydroxide, have already been mentioned (see pp 489 and 493) With *alcoholic* potash phenanthraquinone reacts to give diphenic acid or more complex products[1]

On treatment with nitric acid (sp gr 1 4) at moderate temperatures phenanthraquinone yields a *mono-nitrate*, and with excess of bromine at low temperatures a dibromo addition product Considering the ease with which these compounds lose nitric acid and bromine respectively, it is probable that they are *oxonium compounds* (see Pyrone) of the following structure

$$\underset{\text{Phenanthraquinone nitrate}}{\begin{array}{lcl}C_6H_4 & — & C\ O{<}^{H}_{O\ NO_2}\\ | & & |\\ C_6H_4 & — & C\ O\end{array}} \qquad \underset{\text{Phenanthraquinone dibromide}}{\begin{array}{lcl}C_6H_4 & — & C\ O{<}^{Br}_{Br}\\ | & & |\\ C_6H_4 & — & C\ O\end{array}}$$

[1] R Meyer and Spengler, *Ber*, 1905, 38, 440, 950

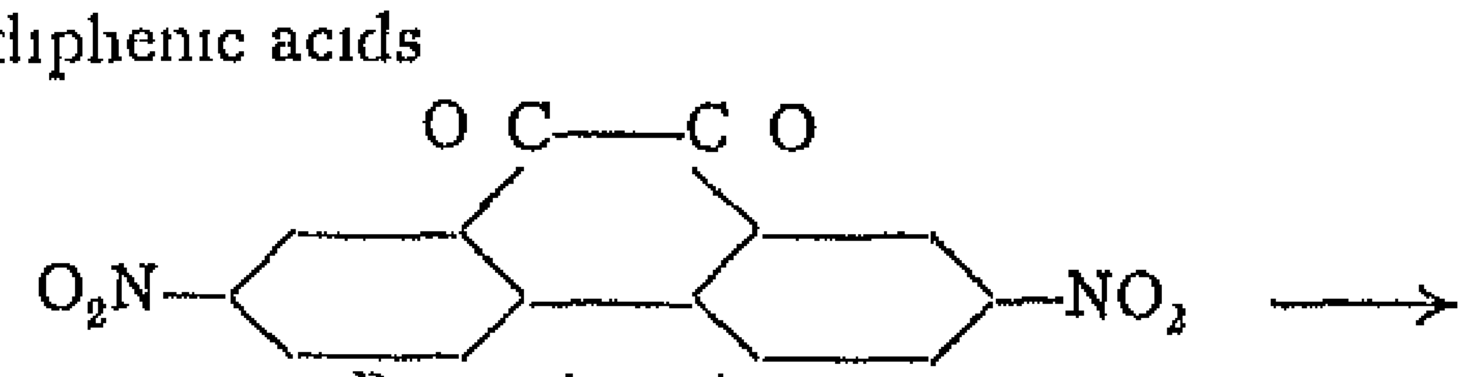
Nitro-derivatives of Phenanthraquinone

All the possible mononitro derivatives are known, with the exception of 1-nitro-phenanthraquinone. Of the dinitro-compounds, the symmetrical 2:7- and 4:5-*dinitro-phenanthraquinones* have been prepared.

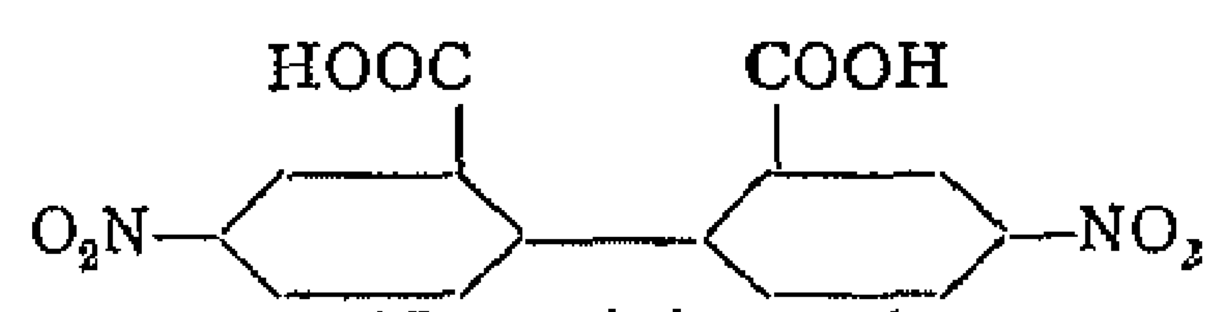
3-*Nitro-phenanthraquinone* has been obtained by Schmidt and Kampf, and its structure confirmed by the oxidation of 3-nitro-phenanthrene.[1] The remaining nitro-compounds have been prepared by direct nitration of phenanthraquinone. When boiled for two to three minutes with concentrated nitric acid of sp. gr. 1·45, the quinone is converted mainly into a mixture of 2- and 4-*nitro-phenanthraquinones*.[2] Energetic nitration yields exclusively the above symmetrical dinitro-derivatives.

There is a tendency for the two symmetrical dinitro-derivatives to be formed by the nitration of any of the mononitro-compounds so far known. The pronounced tendency for substituents to assume the 2:7-positions is also apparent in other substitution reactions.

On oxidation with potassium bichromate and sulphuric acid all nitro-derivatives of phenanthraquinone yield the corresponding nitro-diphenic acids.



2:7 Dinitro-phenanthraquinone



pp'-Dinitro-diphenic acid

In the following table will be found the melting points of all known nitro derivatives of phenanthraquinone, together with those of the corresponding diphenic acids.

Name	Melting point	Name	Melting point
2-Nitro-phenanthraquinone	257-258°	*p*-Nitro-diphenic acid[3]	220-221°
3-Nitro-phenanthraquinone	279-280° (decomp.)	*m*-Nitro-diphenic acid	268°
4-Nitro-phenanthraquinone	179-180°	*o*-Nitro-diphenic acid	248-250° (decomp.)
2:7-Dinitro-phenanthraquinone	301-303°	*pp'*-Dinitro-diphenic acid[4]	253°
4:5-Dinitro-phenanthraquinone	228°	*oo'*-Dinitro-diphenic acid	303° (decomp.)

[1] J. Schmidt and co-workers, *Ber.*, 1902, 35, 3117; 1908, 41, 3679; 1901, 34, 3531.
[2] J. Schmidt and Austin, *Ber.*, 1903, 36, 3730. Schmidt and Kampf, *Ber.*, 36, 3734.
[3] F. J. Moore and C. H. Huntress, *J. A. C. S.*, 1927, 49, 1324.
[4] The compound of melting point 253° contains 1 mol. H_2O.

On reduction with tin and hydrochloric acid the nitro-compounds yield the corresponding *amino-hydro-phenanthraquinones*, which are generally very unstable in the free state and readily undergo oxidation to *amino quinones* The latter can be diazotised and converted in the usual manner into various substitution products of phenanthraquinone

It will thus be seen that the nitro-phenanthraquinones provide the key to the constitution of most of the other substitution products of phenanthraquinone

They have, for example, been of service in determining the constitution of the *bromo-derivatives*[1] These can be obtained partly by direct bromination, and partly by the oxidation of bromo-phenanthrenes On oxidation they yield the corresponding bromo-diphenic acids, as summarised in the following table

Name	Melting point	Name	Melting point
2-Bromo-phenanthraquinone	233-234°	*p* Bromo diphenic acid	238 239°
3-Bromo-phenanthraquinone	268°	*m*-Bromo diphenic acid	257° (decomp)
4-Bromo-phenanthraquinone	126°	—	—
2 7 Dibromo-phenanthraquinone	323°	*pp'*-Dibromo diphenic acid	277-278°

Hydroxy derivatives of phenanthraquinone may be prepared as indicated above from the amino-compounds, or by the oxidation of acylated hydroxy-phenanthrenes Some of these have been of value in identifying the hydroxy-phenanthrenes described earlier, which were obtained by the degradation of morphine, codeine and thebaine

2-*Hydroxy phenanthraquinone*, violet black needles, m p 280° to 283°

3-*Hydroxy phenanthraquinone*, needles resembling alizarin, acetyl derivative, m p 199° to 201°

4-*Hydroxy phenanthraquinone*, dark red needles, acetyl derivative, m p 188° to 189°

4 5-*Dihydroxy-phenanthraquinone*, chars above 400°, dimethyl ether, m p 190° to 191°

2 7 *Dihydroxy-phenanthraquinone*, decomposes above 400°, diacetyl derivative, m p 236°

3 4-*Dihydroxy-phenanthraquinone*, morphol quinone, red, diacetyl derivative, m p 196° Has been obtained synthetically, as already indicated, and also from phenanthrene by way of 3 nitro phenanthraquinone[2]

3-*Methoxy*-4 *acetoxy phenanthraquinone*, **acetyl methyl morphol quinone,**[3] m p 205° to 206°

3 6 *Dimethoxy* 4 *acetoxy phenanthraquinone*, **acetyl thebaol quinone,**[4] m p 203°

2 3 4-*Trihydroxy phenanthraquinone*, m p 185° with decomp

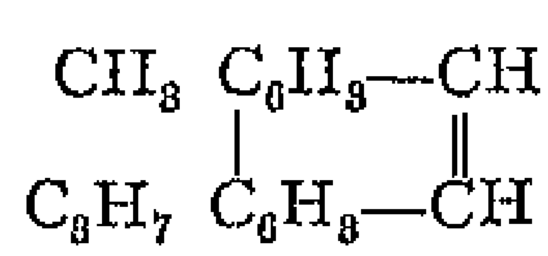
[1] J Schmidt, *Ber*, 1904, **37**, 3551 [2] J Schmidt and Söll, *Ber*, 1908, **41**, 3696
[3] Synthesis, see Pschorr and Vogtherr, *Ber*, 1902, **35**, 4412 [4] Pschorr, Seydel and Stöhrer, *Ber*, 1902, **35**, 4400

The *sulphonic acids of phenanthraquinone* have not yet been investigated in detail 3-Phenanthraquinone-sulphonic acid has been obtained from 3-phenanthrene-sulphonic acid by oxidation with chromic acid [1]

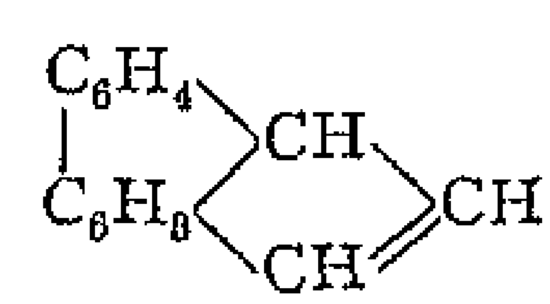
XVII

Other Hydrocarbons containing Condensed Nuclei

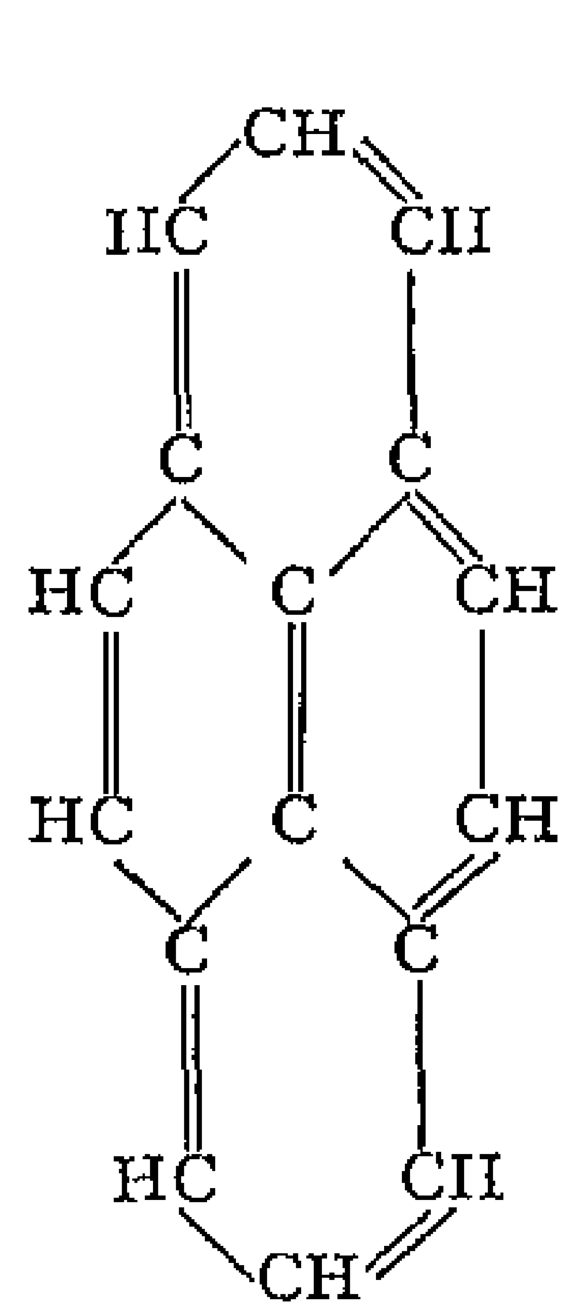
In addition to naphthalene, anthracene and phenanthrene, a number of hydrocarbons of still higher molecular weight are known containing condensed benzene rings These may be described very briefly [2]



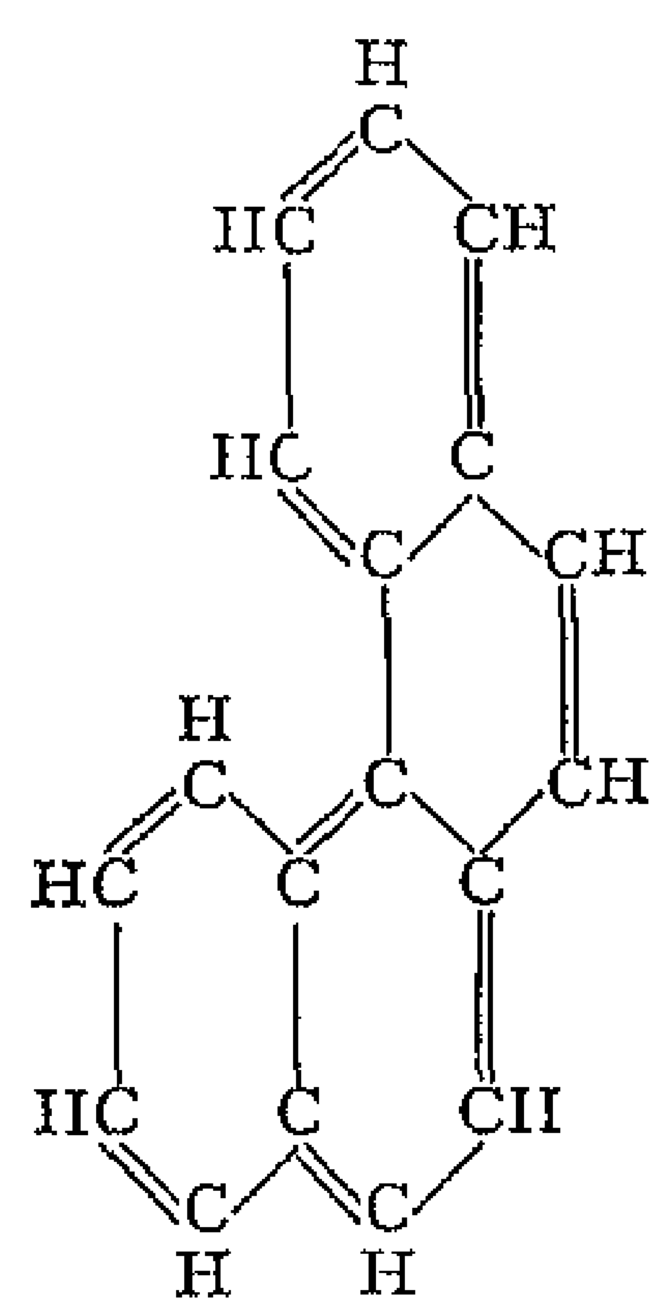
Retene or methyl-isopropyl-phenanthrene
m p 98°, b p 394°



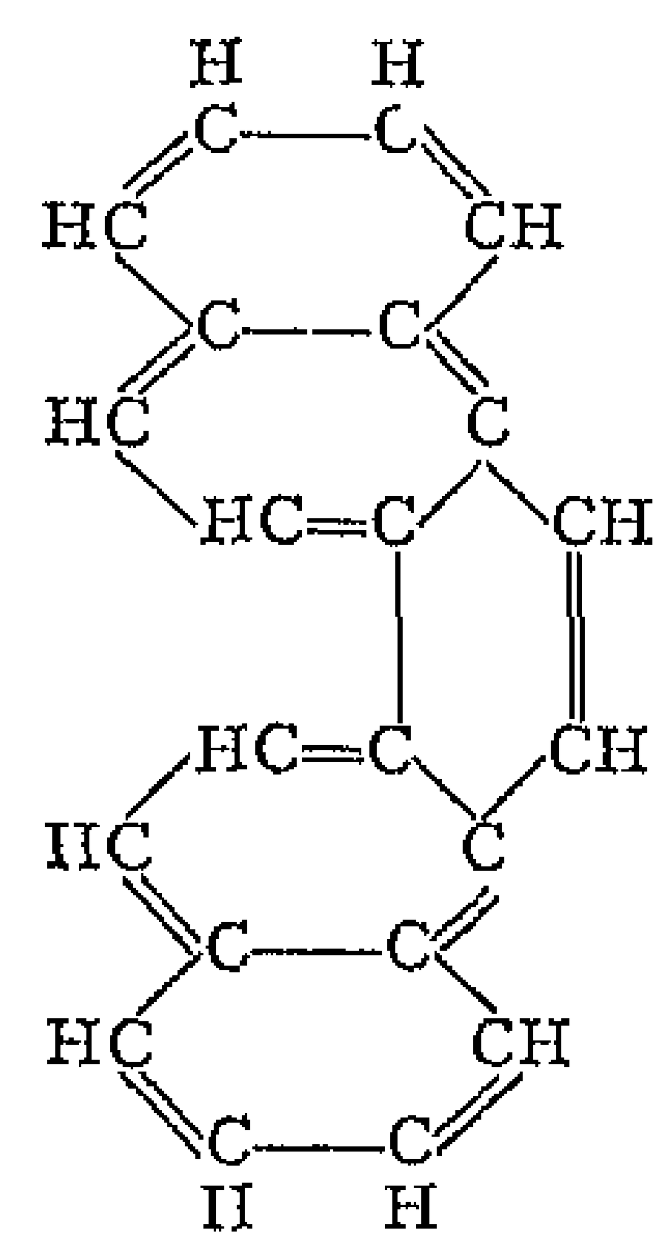
Fluoranthene or Idryl
m p 110°, b p 250° (at 60 mm)



Pyrene
m p 148°, b p 260°/60 mm



Chrysene
m p 250°, b p 448°



Picene
m p 364°

All these compounds are contained in the fraction of coal tar boiling above 360°.

[1] A Werner, *Ann*, 1902, 321, 339 [2] See also *The Higher Coal Tar Hydrocarbons*, by A E Everest (Longmans, Green, 1927) For the hydrocarbons naphthacene, $C_{18}H_{12}$ (m p 335°) and naphthanthracene, $C_{18}H_{12}$ (m p 141), *cf* Gabriel and co workers, *Ber* , 1898, 31, 1272 , 1900, 33, 446

Retene is present in certain fossil coniferous resins found in deposits of peat and brown coal It is formed by the dry distillation of the wood of conifers, and can therefore be obtained from pine tar Part of the retene in these sources probably originates from the diterpene derivative **abietic acid** (m p 153°), which has been isolated from resin or colophonium (p 474) and yields retene on being heated with sulphur[1] *Perhydro-retene* or **fichtelite**, $C_{18}H_{32}$, is also found in fossil coniferous resins[2] Phenanthrene, pyrene and fluoranthene also occur in "Stupp" fat, a by product obtained from the treatment of mercury ores in Idria

In recent years a number of hydrocarbons of this type have been prepared synthetically[3] According to Scholl, the condensation of aromatic nuclei with loss of hydrogen—a process long known in the form of pyrogenic reactions—is greatly accelerated in the presence of aluminium chloride In this way condensation can be satisfactorily effected at as low a temperature as 100°, and the method can therefore be applied to substances which could not survive the drastic conditions of a pyrogenic reaction The practical details have been worked out particularly for the union of aromatic nuclei in cases where elimination of hydrogen leads to the formation of new rings Thus naphthalene has been converted into 1 1′-dinaphthyl, and the latter into **perylene**, $C_{20}H_{12}$, which was obtained in the form of yellow or bronze leaflets of m p 264° to 265°

[1] Veresterberg, *Ber*, 1903, 36, 4200 L Ruzicka and M Pfeiffer, *Helv Chim Acta*, 1925, 8, 635 P Levy, *Ber*, 1926, 59, 1302 [2] An isomeric perhydro retene has also been obtained by the hydrogenation of retene, Ipatiew, *Ber*, 1909, 42, 2093. [3] Scholl and co workers, *Ann*, 1912, 394, 11, 1913, 398, 82, *Ber*, 1922, 54, 109

PART III

Heterocyclic Compounds

REFERENCE has repeatedly been made to the occurrence of cyclic compounds in which the ring systems—unlike those of the carbocyclic series—are composed of other elements in addition to carbon These are generally classed under the name of *heterocyclic compounds* Owing to their close relationship to members of the aliphatic series, certain derivatives of this type have already been described in the aliphatic section, *e g* ethylene oxide, diazo-methane, lactones, anhydrides, cyanuric acid and purine compounds These are readily prepared from open chain compounds, and by rupture of the ring the latter are easily regenerated The ring systems of the compounds about to be described are distinguished by greater stability, *i e*, they are less readily ruptured Most of such rings resemble the benzene nucleus in containing several unsaturated linkages, and in chemical behaviour the heterocyclic compounds also possess many points in common with those of the benzene series

Heterocyclic systems are known in great variety, and their study forms one of the most interesting branches of organic chemistry Only derivatives of ring systems containing carbon in union with the elements oxygen, sulphur and nitrogen will be considered here Compounds of this type in which sulphur has been replaced by selenium, and others which contain arsenic and phosphorus, have also been prepared As in the case of carbocyclic compounds, a distinction is again drawn between rings containing three, four, five, six and a still higher number of atoms The elements which participate with carbon in ring formation are sometimes termed *hetero-atoms*, and according to the number of these present we speak of mono-, di-, or tri-heteroatomic rings, and so on

In connection with the various carbon rings it has been explained on p 350 that the five- and six-membered types are the most stable The same generalisation holds true for heterocyclic rings Heterocyclic compounds containing three- and four-membered rings are relatively unstable, as is shown by the fact that they are difficult to form and readily break up again Those containing five- and six-membered rings, on the other hand, are usually distinguished by

comparatively high stability With rings of greater complexity, of which a few examples are known, the stability again diminishes

It should also be noted that the number of heterocyclic systems is increased still further by the existence of condensed polynuclear types Just as naphthalene is composed of two benzene nuclei, and phenanthrene of a benzene and a naphthalene nucleus, so in the same manner benzene, naphthalene and other rings may condense with heterocyclic systems A complicated example of this kind has already been met with in indanthrene (p 545), and numerous others will be found in connection with quinoline, indole and their derivatives

Special importance attaches to those compounds in which a five or six membered ring containing nitrogen is present This class includes the vegetable alkaloids and antipyrin, of great value in medicine, and dye-stuffs such as indigo Compounds derived from these systems will therefore be treated in greater detail Five-membered rings containing two or more atoms of nitrogen are frequently named with the ending "azole" (pyrazole, triazole, tetrazole) and six-membered rings with the ending "azine" (pyrazine, triazine, tetrazine)

I

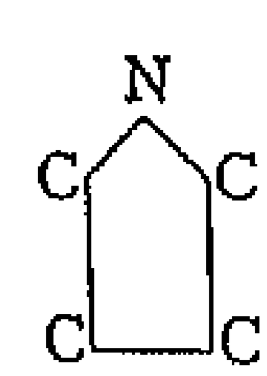
Pyrrole, Furane and Thiophene Groups

The heterocyclic compounds pyrrole, furane and thiophene (see also pp 248 and 251), which stand in close relationship to one another, will be described first

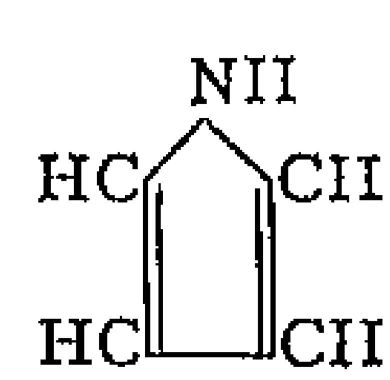
I—PYRROLE GROUP[1]

Among five-membered ring systems containing nitrogen, the pyrrole group stands out prominently Included under this heading are all those chemical compounds, the molecules of which contain a ring built up of four carbon atoms and a nitrogen atom (I)

I



II



The presence of this ring has now been established in a series of important vegetable bases, which had previously been regarded solely

[1] A detailed description of these compounds will be found in a monograph by J Schmidt, *Die Chemie des Pyrrols und seiner Derivate* (Enke, Stuttgart, 1904). See also Ciamician, *Ber*, 1904, 37, 4201

as derivatives of the six-membered ring compound pyridine, viz, nicotine, hygrine, cuskhygrine, atropine, hyoscyamine, cocaine, tropacocaine and others Further, E Fischer has obtained pyrrolidine-2-carboxylic acid as a hydrolytic product of various proteins, and other investigators, including Willstatter, have proved that hæmoglobin and chlorophyll are pyrrole derivatives, thus revealing an interesting connection between the colouring matter of blood and leaves

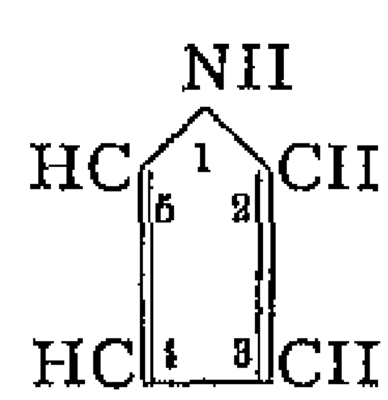
The above examples provide sufficient illustration of the importance of pyrrole derivatives

Pyrrole itself, the parent substance of this class, was first discovered in coal tar and bone tar, and is also present among the distillation products of bituminous shale Baeyer was the first to advance the formula (II) now generally accepted for pyrrole

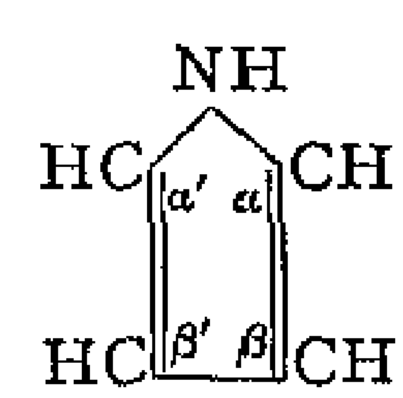
The structural resemblance between pyrrole compounds and those of furane and thiophene has been clearly demonstrated by the work of L Knorr and Paal, on the formation of these compounds from γ-diketones or their enolic modifications This is described more fully below

Nomenclature of Pyrrole Derivatives—The position of substituents in the pyrrole nucleus is usually indicated by the numbers 1 to 5, as in formula III

III



IV



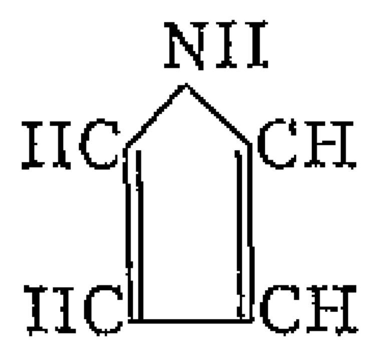
Another system makes use of the letters α, β, as in IV Since positions α and α' are equivalent, and also positions β and β', it is often convenient to distinguish mono-substitution products as α- or β-compounds respectively Derivatives containing a substituent attached to nitrogen are frequently described as N-compounds

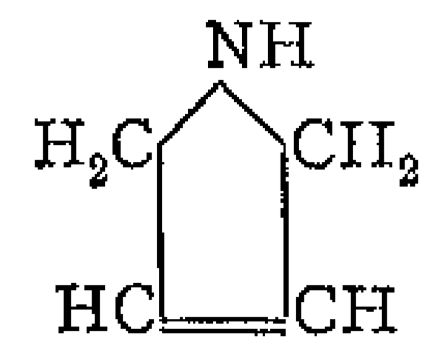
From the above it is seen that each C-monosubstitution product of pyrrole can exist in two isomerides, as an α- or β-derivative Each C disubstitution product can occur in four modifications, viz, as an $\alpha\alpha'$-$\alpha\beta$-, $\alpha\beta'$- or $\beta\beta'$-derivative

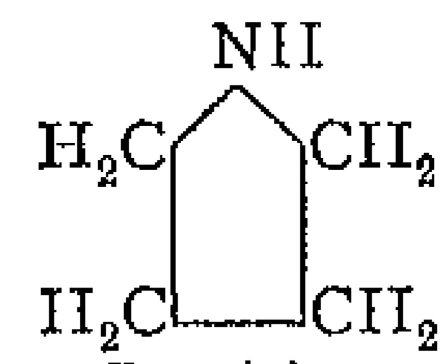
Dihydro-pyrroles are known as *pyrrolines*, and the completely reduced tetrahydro-pyrroles as *pyrrolidines*

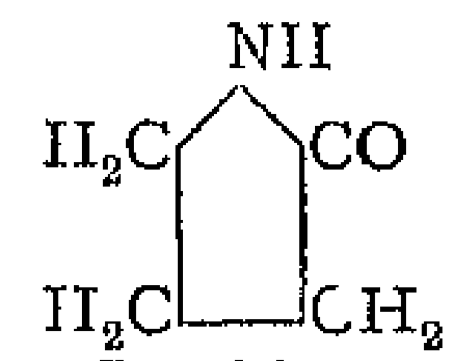
Keto-pyrrolines are termed *pyrrolones*, and keto-pyrrolidines are described as *pyrrolidones* Distinctions are also drawn between various pyrrolones and pyrrolidones, according to the position and number of keto-groups in the molecule The term "pyrrolidone" is commonly used to describe 2-keto-pyrrolidine Substances derived from it can be described either as 2-keto-pyrrolidine or as α-pyrrolidone derivatives, and may be regarded as lactams of γ-amino-acids The

imides of the succinic acid group, of which succinimide itself is the simplest representative, are aa'- or 2 5-diketo-pyrrolidines


Pyrrole

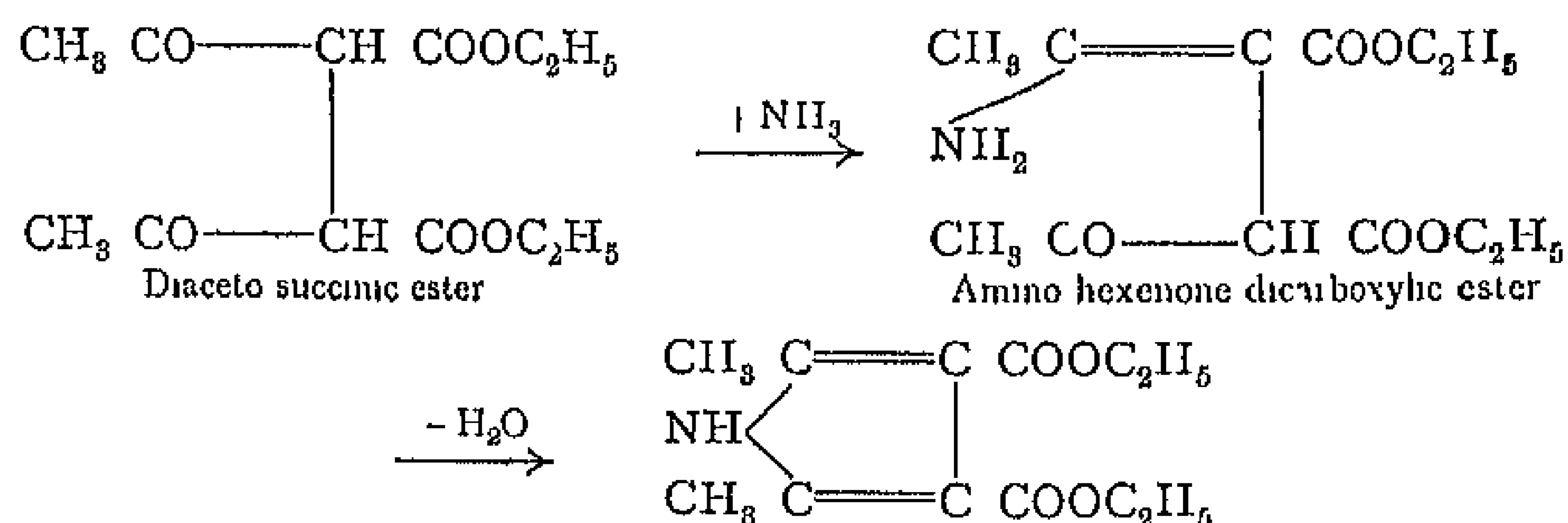

Pyrroline


Pyrrolidine


Pyrrolidone

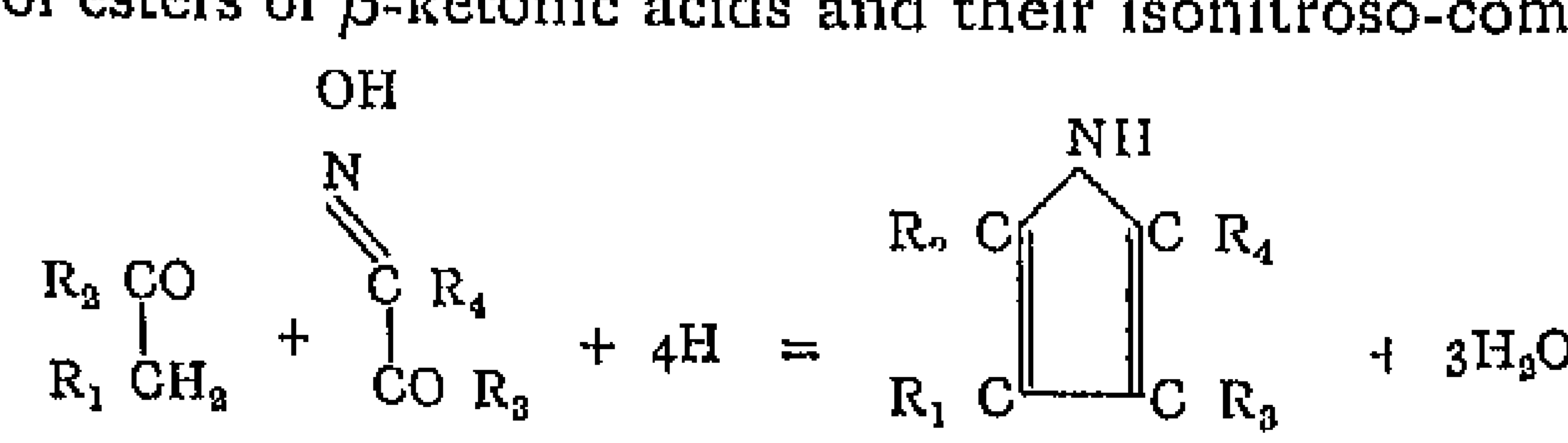
Methods of Forming Pyrrole and Reduced Pyrrole Derivatives

1 The 1 4-diketones, when treated with ammonia or primary amines, are transformed with great ease into pyrrole derivatives This synthesis is effected with equal readiness when the reagents are dissolved in glacial acetic acid, water or ether, and appears to depend on the intermediate formation of amino-ketones (Knorr)[1]


Diaceto succinic ester — Amino hexenone dicarboxylic ester — 2 5 Dimethylpyrrole 3 4 dicarboxylic ester

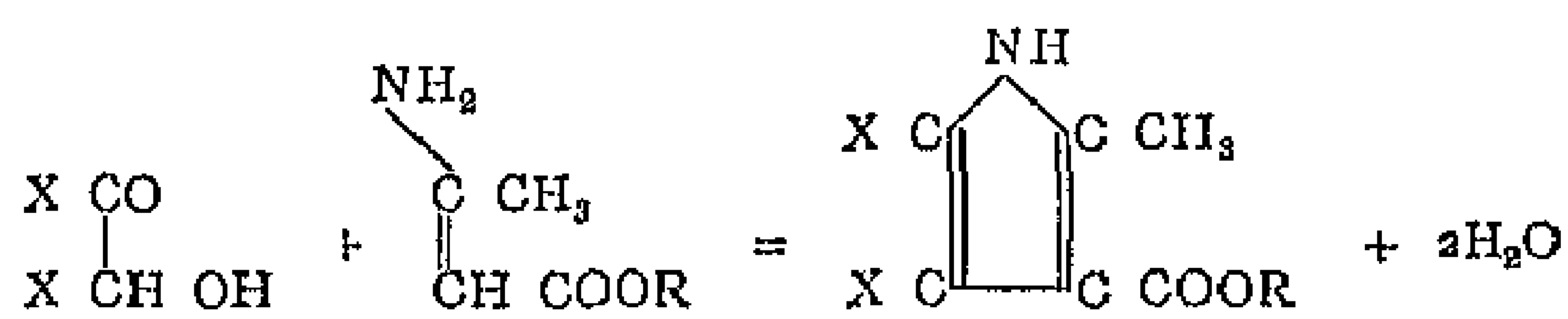
This reaction has proved of service in the preparation of a great number of pyrrole derivatives Any γ-diketo-compound of the general formula R CO CH_2 CH_2 CO R may be employed, and the place of ammonia may be taken by primary amines, amino-acids,[2] hydroxylamine or phenyl hydrazine

2 A second synthesis of pyrrole is also due to L Knorr, who succeeded in preparing 2 4 dimethyl-pyrrole-3 5-dicarboxylic ester by reducing an equimolecular mixture of iso-nitroso-acetoacetic ester and acetoacetic ester by means of zinc dust and glacial acetic acid[3] In a similar manner other pyrrole derivatives were prepared by reducing mixtures of esters of β-ketonic acids and their isonitroso-compounds



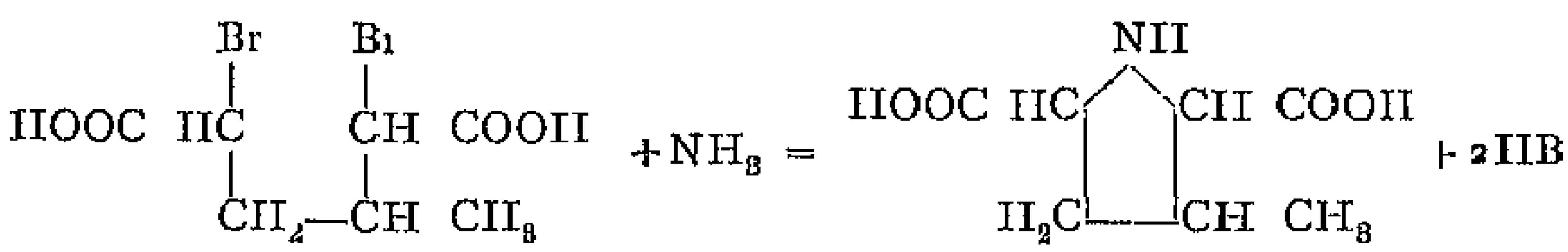
[1] L Knorr and Rabe, *Ber*, 1902, 35, 3801 W. Borsche and Fels, *Ber*, 1906, 39, 3877 Since many pyrrole derivatives give a red coloration with a pine splint moistened with hydrochloric acid, the above method of preparing pyrroles may be used as a test for 1 4-diketones (*cf* p 251) [2] J Schmidt and Schall, *Ber*, 1907, 40, 3002 [3] L Knorr, *Ann*, 1886, 236, 296 *Ber*, 1902, 35, 2998 Piloty, *Ber*, 1910, 43, 489

3 In certain cases the reduction of a mixture of an amino acid ester (*e g*, amino crotonic ester) with a 1 2 diketone also leads to the formation of derivatives of pyrrole[1] Reduction may be dispensed with altogether if the diketone is replaced by a 1 2 keto-alcohol of the type of benzoin, *e g*



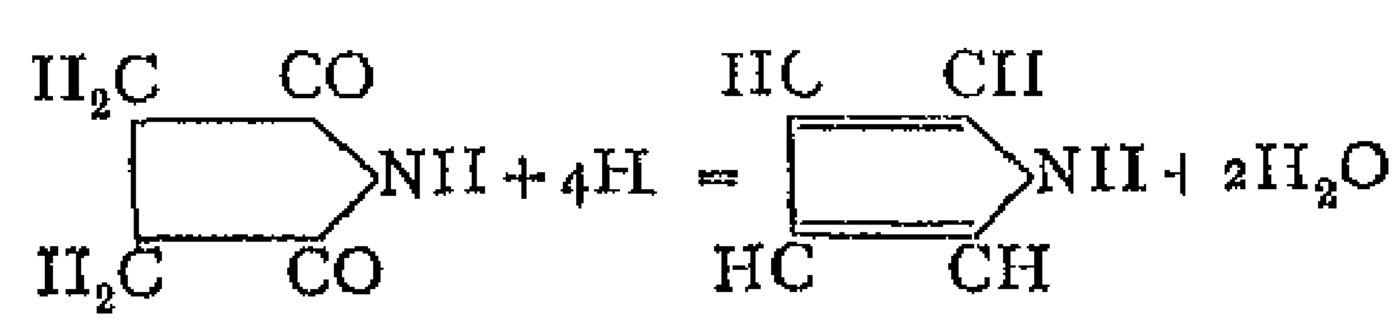
4 A method first used by Hantzsch is to treat β ketonic esters with chloro acetone and ammonia, when pyrrole carboxylic esters are formed[2]

5 Willstatter[3] has shown that the action of ammonia or alkyl amines on 1 4-dibromo-acids of the aliphatic series readily yields carboxylic acids of pyrrolidine



In a similar manner pyrrolidine derivatives can be obtained by the interaction of primary amines and 1 4-dibromo-derivatives of hydrocarbons

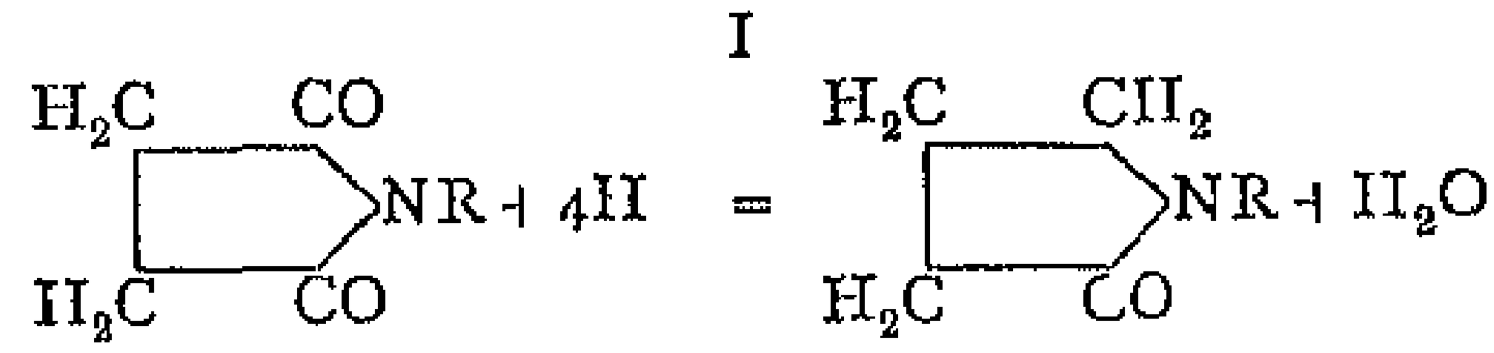
6 Another method of general applicability is based on the reduction of succinimide to pyrrole by means of zinc dust and acetic acid, or hydrogen and heated platinum sponge (Bell and Bernthsen)



In the same manner substituted pyrroles are formed by the reduction of a variety of acid imides and lactams (which may also be regarded as keto-derivatives of hydrogenated pyrroles)

Different results are obtained by reducing succinimide and its substitution derivatives by electrolytic means[4] (Tafel) In this case the corresponding pyrrolidone is formed (formula I), together with very small amounts of pyrrolidine

I



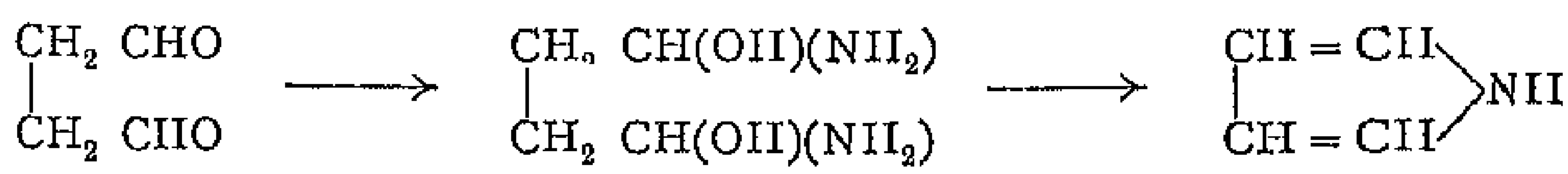
[1] F Feist, *Ber*, 1902, 35, 1558 [2] A Hantzsch, *Ber*, 1890, 23, 1474 *Cf also* Korschun, *Ber*, 1905, 38, 1125 [3] *Ber*, 1899, 32, 1290, 1900, 33, 1160, 1901, 34, 1818, 1902, 35, 620, 2065 *Ann*, 1903, 326, 91 [4] Tafel, *Z phys Ch*, 1906, 54, 433 B Emmert, *Ber*, 1907, 40, 912

Since succinimides are readily prepared in quantity,[1] this process also renders the pyrrolidones easy of access

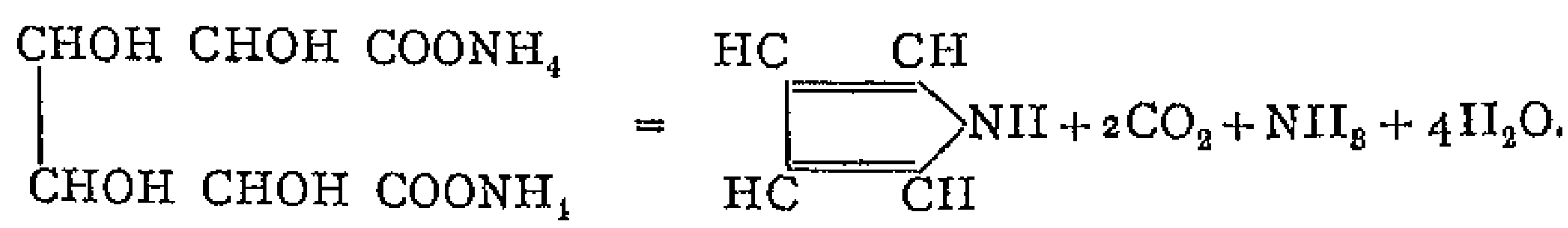
7 On being heated with phosphorus pentachloride, succinimide and the imide of dichloro-maleic acid readily yield chlorinated products, which on reduction give tetrachloro-pyrrole By way of the tetra iodo compound the latter may be converted into pyrrole

Pyrrole itself is also obtained

8 By the condensation of succindialdehyde with ammonia,[2] this is the simplest case of the reaction given under method 1, p 564 An addition compound is first produced

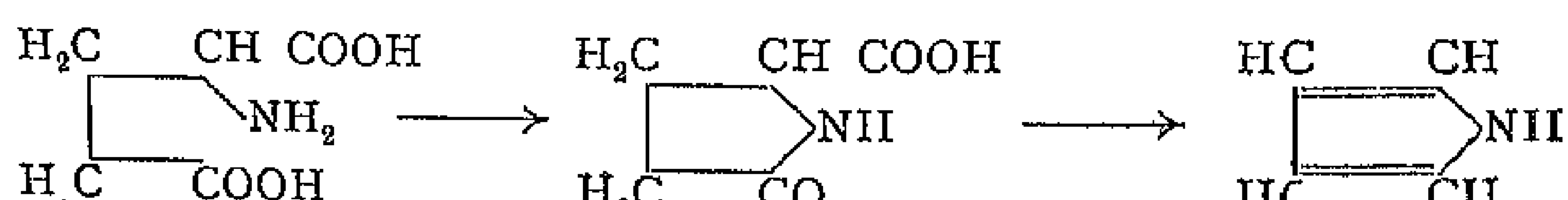


9 From the ammonium salt of saccharic or mucic acid by distillation, or better by heating with glycerol to 200°[3]



The use of substituted mucic acids leads to the formation of substituted pyrroles[4]

10 In a similar manner pyrrole has been obtained from glutamic acid and its calcium salt



Glutamic acid   Pyroglutamic acid

11 Pyrrole is also formed by leading a mixture of acetylene and ammonia through a tube heated to dull redness

$$2C_2H_2 + NH_3 = C_4H_5N + H_2$$

This reaction explains the occurrence of pyrrole in tar

1 Compounds of the Pyrrole Series

PYRROLE AND ITS GENERAL PROPERTIES

Pyrrole, C_4H_4NH The occurrence (p 563) and formation (p 564) of pyrrole have already been treated from the general standpoint

The *preparation of pyrrole* is best effected from bone tar This is fractionated several times, freed from strongly basic substances by

[1] Compare Koller, *Ber*, 1904, 87, 1598 [2] Harries, *Ber*, 1901, 34, 1488, 1902, 35, 1179 [3] E Khotinsky, *Ber*, 1909, 42, 2506 [4] For the mechanism of this reaction see Pictet and Steinmann, *C*, 1902, I, 1297

shaking with dilute acid, and again fractionated Pyrrole distils over in the fraction boiling between 98° and 150°, and may be purified by conversion into the solid potassium compound

Pyrrole is a colourless liquid which turns brown in air and smells somewhat like chloroform It boils at 130° to 131° under 761 mm , sp gr 0 9752 at 12 5° It dissolves sparingly in water but is readily soluble in alcohol and ether It is insoluble in aqueous alkalis and only dissolves slowly in acids On long standing or warming in acid solution a red flocculent precipitate of a substance known as *pyrrole red* separates

In pyrrole vapour a pine splint moistened with hydrochloric acid is coloured a pale red, which rapidly changes to an intense carmine red This reaction is employed as a test for pyrrole (see p 251)

In the presence of dilute acids pyrrole readily unites with a number of compounds containing the group —CO CO— (such as phenyl glyoxalic acid, benzil, phenanthra quinone, and alloxan) with the formation of dye stuffs

Salt Formation with Pyrrole—Pyrrole is a very weak base which dissolves slowly in dilute acids With strong acids it is rapidly resinified Even from solutions in dilute acids it is only possible to isolate definite simple salts in a few cases, and resinification readily takes place This action of acids on pyrrole is probably due to polymerisation (see below)

Pyrrole combines with picric acid to give a very unstable picrate With certain metallic salts[1] it yields double compounds

Salt formation can only be established definitely with derivatives of pyrrole which are stable towards strong acids Chief among these are derivatives of dimethyl pyrrole containing acetyl or esterified carboxylic acid groups The negative radicals make the ring more resistant, and at the same time the methyl groups increase the basic properties In its power of forming salts, pyrrole may be compared to diphenylamine

Pyrroles are aromatic in character and possess points in common with both phenols and aromatic amines, as may readily be seen from their reactions

The analogy with phenols is shown by the similarity in behaviour of the NH group in pyrrole with that of the phenolic hydroxyl group Potassium, for example, reacts with pyrrole with evolution of hydrogen and formation of a solid *potassium compound*, C_4H_4NK Pyrroles, like phenols, readily couple up with diazonium salts to give azo-compounds In this case the azo-group assumes an α-position, or if both of these are occupied, a β position Thus pyrrole and benzene diazonium chloride yield *pyrrole-azobenzene*, C_6H_5 N N C_4H_3 NH, and *pyrrole disazobenzene*, C_6H_5 N N (C_4H_2.NH) N N C_6H_5, in which

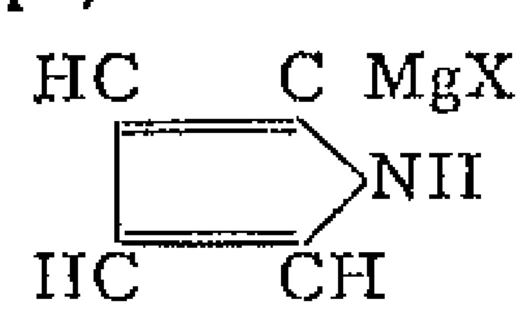
[1] For a double compound of pyrrole with nickelous ammonium cyanide, see Hofmann and Arnoldi, *Ber* , 1906, 39, 341

the azo-groups are in the α-positions The analogy with phenols is also borne out in the behaviour of pyrroles towards nitrous and nitric acids. In particular, the nitroso-pyrroles exhibit tautomeric phenomena similar to those shown by the nitroso-phenols (p 425) Nitroso-pyrrole itself is a very unstable substance and can only be obtained in the form of its sodium compound, $C_4H_3(\ N\ ONa)N$

Pyrrole, like phenol and aniline, is readily substituted by halogens, all of the four methine hydrogen atoms being replaceable The most important halogen derivative is tetra-iodopyrrole, which is described later

The similarity of pyrrole to aniline is specially evident in its behaviour on alkylation (see below)

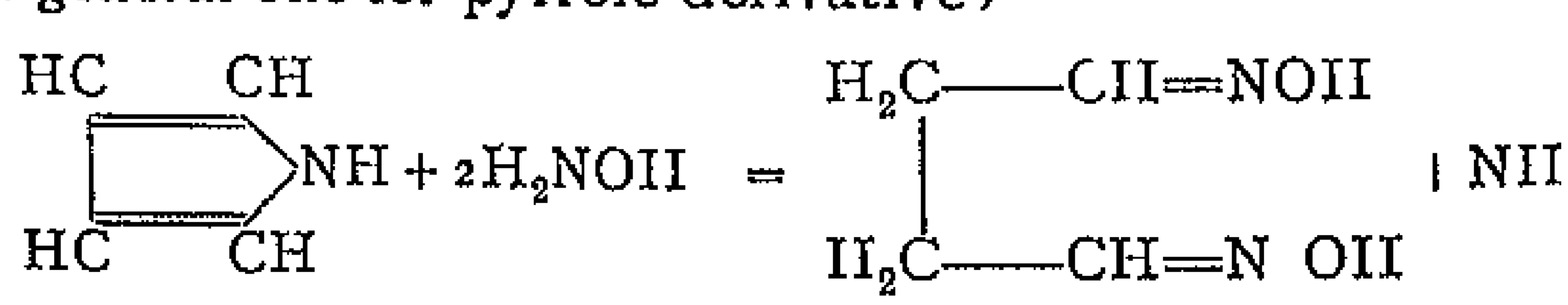
Organo-magnesium halides react with pyrrole to form magnesium pyrrole compounds of the type,[1]



These are useful for the synthesis of pyrrole derivatives having side chains in the α-position With carbon dioxide, for example, they give pyrrole-α-carboxylic acids

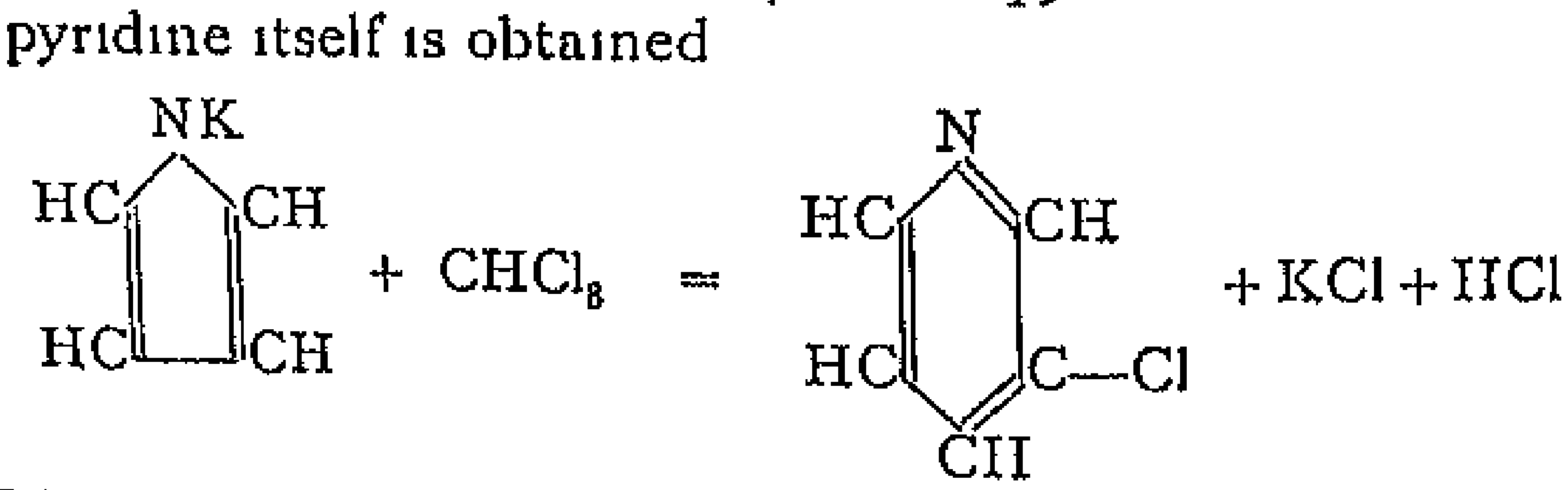
Opening of the Pyrrole Ring by Means of Hydroxylamine

It has been shown by Ciamician that when hydroxylamine reacts with pyrrole the ring is opened and succindialdoxime formed This reaction is the reverse of the synthesis quoted on p 566, and appears to be a general one for pyrrole derivatives



Transformation of the Pyrrole Ring into the Pyridine Ring

When pyrrole or potassium pyrrole is heated with sodium ethoxide and chloroform, there is formed *β chloro-pyridine*[2] With methylene iodide, pyridine itself is obtained

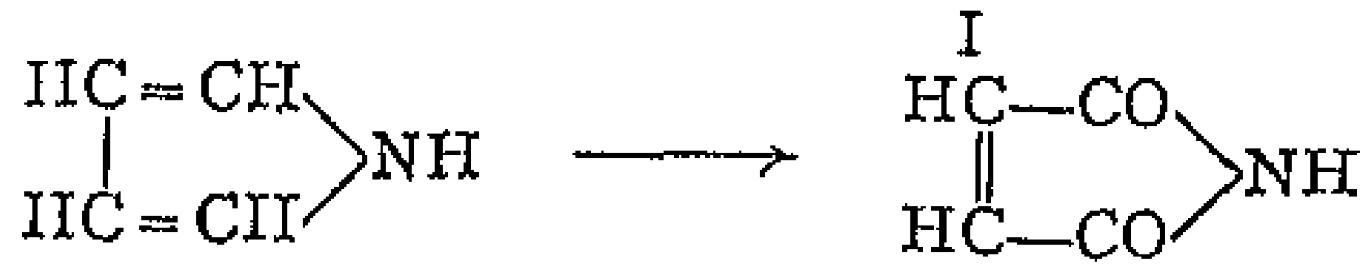


[1] B Oddo, *Gazz chim ital*, 1910, 39, I, 649 [2] Ciamician and Dennstedt, *Ber*, 1881, 15, 1172 Ciamician and Silber, *Ber*, 1884, 18, 724 *Cf also* Plancher and Carrasco, *C*, 1905, I, 1155

This is a general reaction for pyrrole, and is also given by its homologues[1] and the indoles (p 591)

Oxidation with chromic acid mixture converts pyrrole into the imide of maleic acid (I),

I



In a similar manner substituted pyrroles, particularly the chloro- and bromo-derivatives, are oxidised to substituted maleic derivatives

This oxidation has recently been recognised as a valuable means of determining the orientation of substituents in the pyrrole nucleus and also for detecting the presence of a pyrrole ring in substances of unknown constitution For example, the pyrrole nature of hæmatin has been demonstrated by oxidising the latter to a compound $C_8H_9O_4N$, which proved to be a substituted imide of maleic acid

Tripyrrole, $(C_4H_5N)_3$, is formed under certain conditions[2] from pyrrole in the presence of hydrochloric acid When heated to 300°, tripyrrole decomposes into ammonia, pyrrole and indole[3]

Other polymers obtained from alkyl pyrroles break up in a similar manner, and the process therefore represents *a passage from the pyrrole to the indole series*

N-Substituted Pyrroles[4]

Potassium pyrrole, C_4H_4NK, is one of the most important derivatives of this type and has been repeatedly mentioned in the foregoing pages It is formed together with hydrogen when potassium is dissolved in pyrrole, and also on boiling pyrrole with solid caustic potash A sodium compound cannot be obtained by these methods

The potassium compound is the starting material in the preparation of a number of N-derivatives of pyrrole, since it reacts readily with various halogen compounds, *e g*,

$$C_4H_4NK + I\cdot CH_3 = C_4H_4N\cdot CH_3 + KI$$

N-Alkyl-pyrroles are also produced by the above pyrrole syntheses by using alkyl amines in place of ammonia The N-alkyl-pyrroles resemble pyrrole in having feebly basic properties They do not unite with alkyl iodides and are less reactive than pyrrole

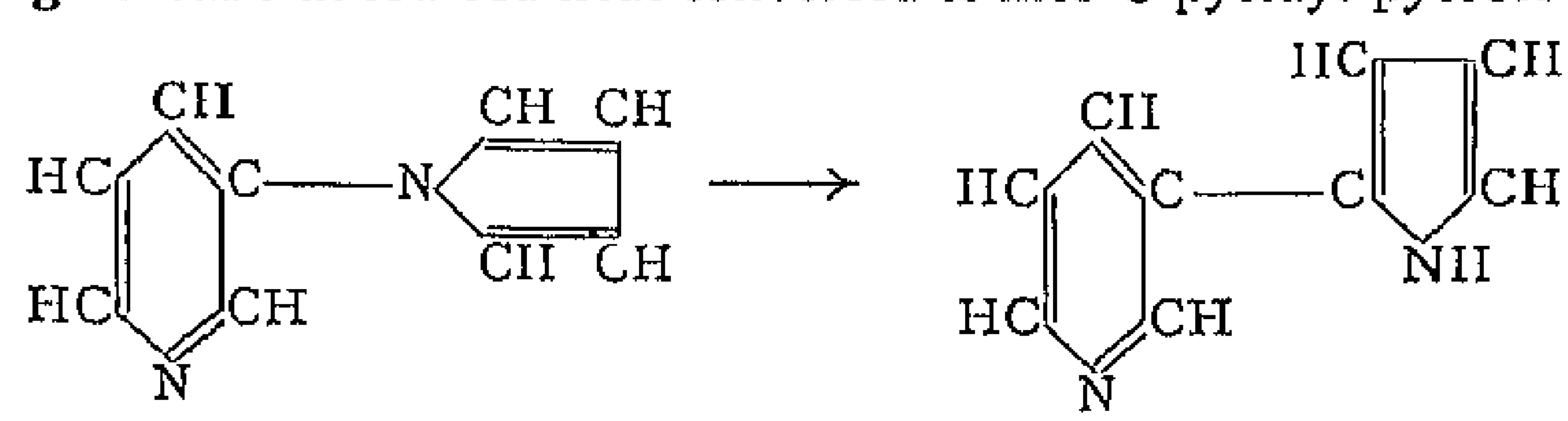
[1] Bocchi, *Gazz chim ital*, 1900, 30, I, 89 Ciamician, *Ber*, 1904, 37, 4231 [2] Dennstedt and Zimmermann, *Ber*, 1888, 21, 1478 [3] Dennstedt and Voigtlander, *Ber*, 1894, 27, 479 [4] The replaceability of the imide hydrogen atom and the phenolic nature of the pyrroles is supposed to be due to the acidic character of the two C=C groups present in the molecule Marckwald, *Ann*, 1894, 274, 10 *Ber*, 1895, 28, 1501 Erlenmeyer, jun, *J pr Ch*, 1900, 62, 145

Wandering of Groups from Nitrogen to Carbon

A point of special interest is that N-derivatives of pyrrole are transformed under the influence of heat into C-derivatives, in the same way as alkylated anilines are converted into homologues of aniline (p 380)

$$C_4H_4\,N\,CH_3 \longrightarrow H_3C\,C_4H_3\,NH$$

Pictet and Crepieux,[1] for example, by distilling N-pyridyl-pyrrole through a tube at low red heat converted it into C-pyridyl-pyrrole



This conversion formed one of the stages of Pictet's synthesis of nicotine

The N-alkyl-pyrroles have lower melting- and boiling-points than the corresponding C-derivatives

C-Substituted Pyrroles.

Among the *halogen derivatives* of pyrrole the most important is tetra-iodopyrrole or **iodole**, $C_4I_4\,NH$ It was first prepared by the action of an ethereal solution of iodine on potassium pyrrole (Ciamician and Dennstedt) Later, it was discovered that it could be obtained from pyrrole, potassium hydroxide and iodine, and also directly from pyrrole and iodine in the presence of indifferent solvents It is employed therapeutically in the treatment of wounds in place of iodoform, over which it possesses the advantage of being odourless and less poisonous, although milder in action It forms shining, yellowish-brown leaflets, which on being heated decompose between 140° and 150°, without melting When reduced with potassium hydrate and zinc dust, tetra-iodopyrrole is converted into pyrrole With nitrous or nitric acids it yields nitro-derivatives

Homologues of Pyrrole—C-Alkyl-pyrroles are present with pyrrole in bone oil Their occurrence thus corresponds exactly to that of toluene and the xylenes in coal tar They may be obtained synthetically by reactions already described in the previous pages, and are of interest in connection with the structure of hæmoglobin and chlorophyll

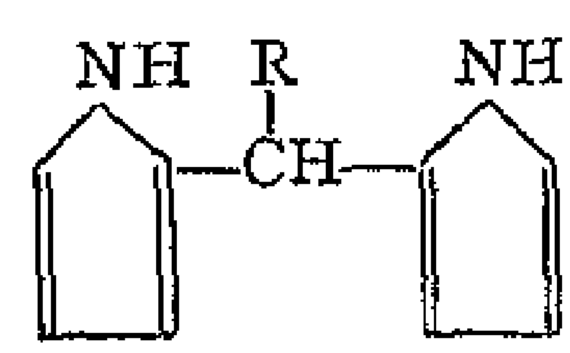
Pyrryl magnesium bromide, which is formed with evolution of ethane by the action of magnesium on pyrrole and ethyl bromide in ethereal solution, can also be used in the preparation of alkyl-pyrroles

[1] *Ber*, 1895, 28, 1905

On interaction with allyl iodide, for example, this compound yields *α-allyl- and αα'-diallyl-pyrrole*[1] By treatment with sodium alcoholates it is possible to introduce methyl and ethyl groups into substituted pyrroles[2]

C-Alkyl-pyrroles possess the same chemical character as pyrrole itself and give the same colour reactions In air they change more rapidly than pyrrole, and although resinified with acids are somewhat more stable in this respect than the parent compound

Pyrrole derivatives with a methyl group in the α-position, and containing at least one unsubstituted nuclear hydrogen atom, have been shown to undergo condensation with aromatic aldehydes[3] The aldehydes, however, do not attach themselves to the α-methyl group, as is the case with α-substituted pyridine derivatives (see index), nor does the imino-group enter into reaction Two nuclear hydrogen atoms from two pyrrole molecules are eliminated with the aldehydic oxygen atom in the form of water, and the residues unite to give dipyrryl-aryl-methane derivatives of the general formula,



in which the coupling may take place in the α- or β-position of pyrrole

Pyrrole Derivatives from the Colouring Matter of Blood and Leaves[4]

It is well known that the colouring matter of blood is the *hæmoglobin* present in the red corpuscles In contact with air this takes up one molecule of oxygen and is transformed into oxyhæmoglobin The colouring matter of blood is always isolated in the form of this simple derivative, except when air is very carefully excluded

Oxyhæmoglobin is soluble in water, from which it can be precipitated as a brilliantly red crystalline compound by the addition of alcohol It is composed of two parts, namely the actual dye-stuff, oxyhæmatin, and the albuminous component, globin, united with it Glacial acetic acid breaks up oxyhæmoglobin to give the coloured product *oxyhæmatin*, $C_{34}H_{32}N_4O_4FeOH$ If sodium chloride is also present, a hydroxyl group of oxyhæmatin is replaced by chlorine and *hæmin*, $C_{34}H_{32}N_4O_4FeCl$, is formed Hæmin thus appears to be the chloride of oxyhæmatin

Hæmoglobin (reduced hæmoglobin) contains the globin in union

[1] K Hess, *Ber*, 1913, 46, 3125 [2] H Fischer and Bartholomæus, *Zeit physiol Ch*, 1912, 80, 6 [3] F Feist, *Ber*, 1902, 35, 1647 [4] W Küster, "Über den Blutfarbstoff," *Ber*, 1911, 21, 506 R Willstätter, "Über Pflanzenfarbstoffe," *Ber*, 1914, 47, 2831 H Fischer, "Über Blutfarbstoff und einige Porphyrine," *Zeit angew Chem*, 1925, 38, 981, "Über Porphyrine und ihre Synthesen," *Ber*, 1927, 60, 2611

with *reduced hæmatin*, in which the iron is in the ferrous state. An important advance was made in 1926 when Hill and Holden[1] successfully separated the *natural* globin from hæmoglobin and showed that this undenatured protein combined with neutral oxyhæmatin (p_H 5 to 10) to form *methæmoglobin* (see p. 773). Similarly with reduced hæmatin (p_H 9.0) it yields hæmoglobin itself. On the other hand, *denatured* globin unites with reduced hæmatin to give *hæmochromogen*[2]

Hæmin can be obtained in the crystalline state by adding blood to a hot saturated solution of salt in glacial acetic acid. It is a tetra pyrrole iron complex containing the oxygen in the form of two free carboxyl groups.

When iron is removed from hæmin or hæmatin, compounds known as **porphyrins** are obtained. According to the acid reagent employed for this purpose (conc. H_2SO_4, HCl, HBr in glacial acetic acid) the resulting porphyrins exhibit minor differences in composition. They are readily identified spectroscopically and can be again transformed into their complex iron salts, **hæmins**, which show a close spectroscopic resemblance to natural hæmin. Iron can usually be introduced without difficulty so that hæmins and porphyrins must have similar molecular structures. Porphyrins are also found in the living organism.

Hence it will be seen that reliable information as to the nature of hæmoglobin may also be obtained by investigating the iron-free hæmatoporphyrin.

Among earlier researches on the constitution of hæmin three degradation methods have proved of great value:

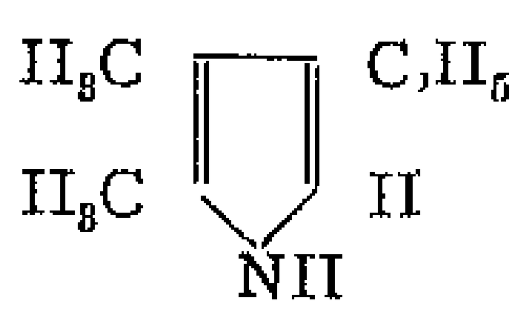
1. Reduction with hydriodic acid in glacial acetic acid, first employed by Nencki
2. Kuster's oxidative process, and
3. Disruption by alkylation as carried out by Hans Fischer and Rose.

The most successful disruptive method is the *reduction with hydriodic acid and acetic acid*. By treating hæmin in this manner Nencki obtained **hæmopyrrole**, which he regarded as a uniform product and isolated in the form of a mercury chloride compound and of a picrate. The occurrence of acid constituents in the reduction mixture was first established by Piloty, who isolated **hæmopyrrole carboxylic acid** by employing tin and hydrochloric acid as reducing agents. Nencki's method was subsequently re-examined by Willstatter, Hans Fischer and also by Piloty. As a result it was found that the hæmopyrrole of Nencki was not a homogeneous product but a complicated mixture. Other acid components were also discovered associated with hæmopyrrole-carboxylic acid. A complete summary of the reductive

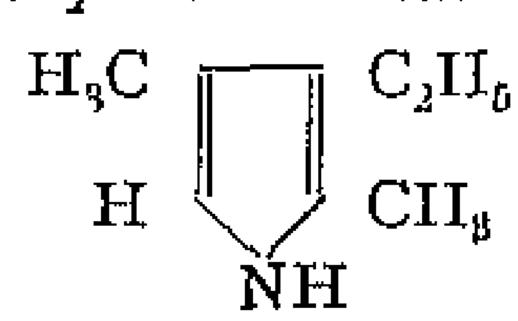
[1] Hill and Holden, *Biochem. J.*, 1926, 20, 1326. [2] Anson and Mirsky, *J. Physiol.*, 1925, 60, 50; see, however, *Ann. Rep. Chem. Soc.*, 1927, 265, 267.

disruption products of hæmin isolated by these methods is given below

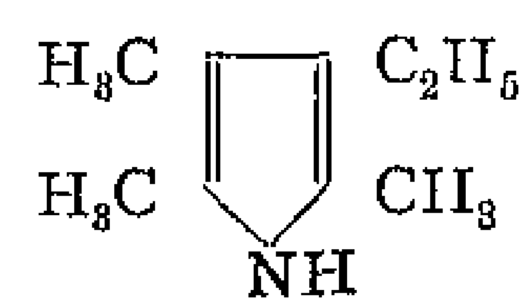
Reductive Disruption Products of Hæmin Hæmopyrrole Bases



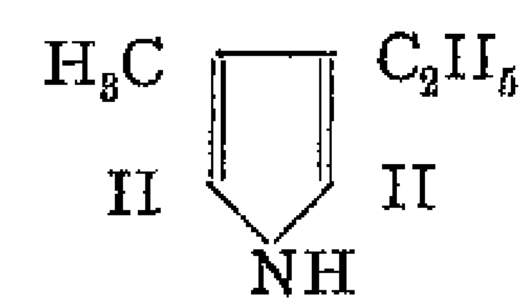
1 Hæmopyrrole



2 Kryptopyrrole

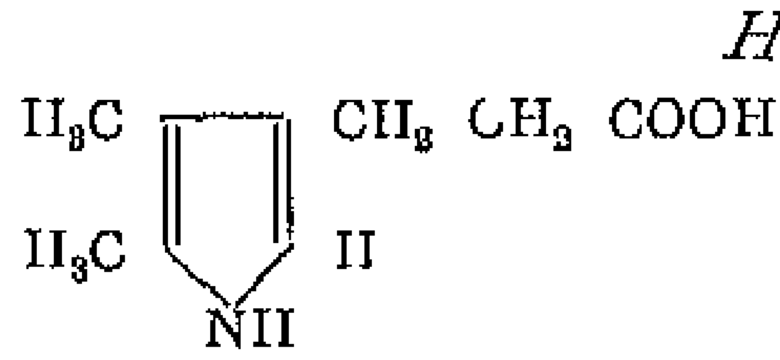


3 Phyllopyrrole

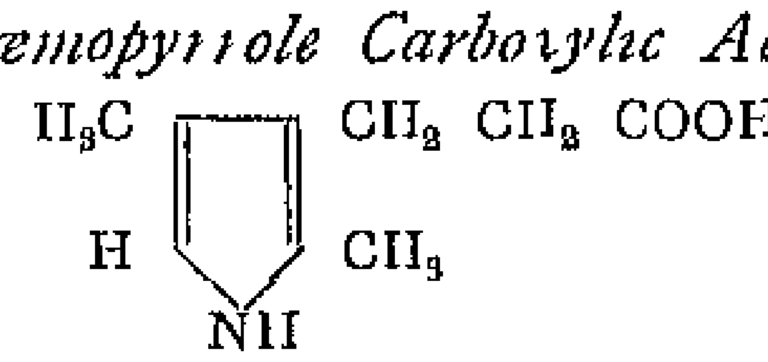


4 Opsopyrrole

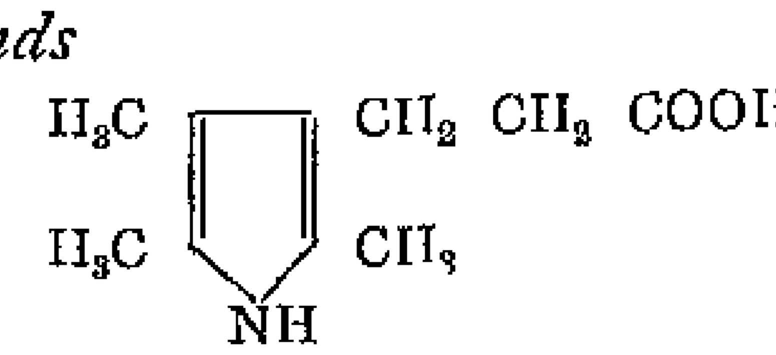
Hæmopyrrole Carboxylic Acids



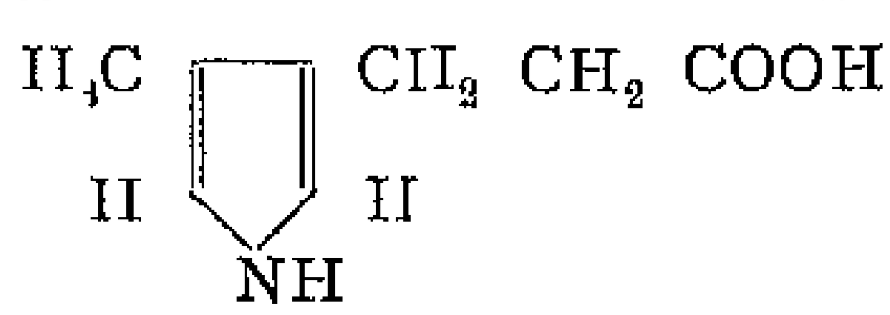
5 Hæmopyrrole carboxylic acid



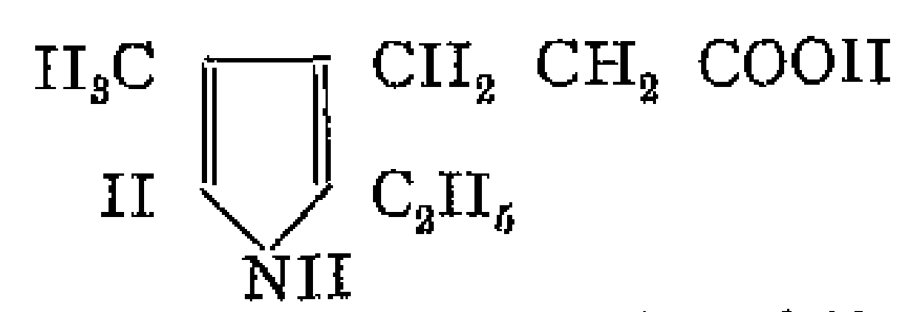
6 Kryptopyrrole carboxylic acid



7 Phyllopyrrole carboxylic acid



8 Opsopyrrole carboxylic acid

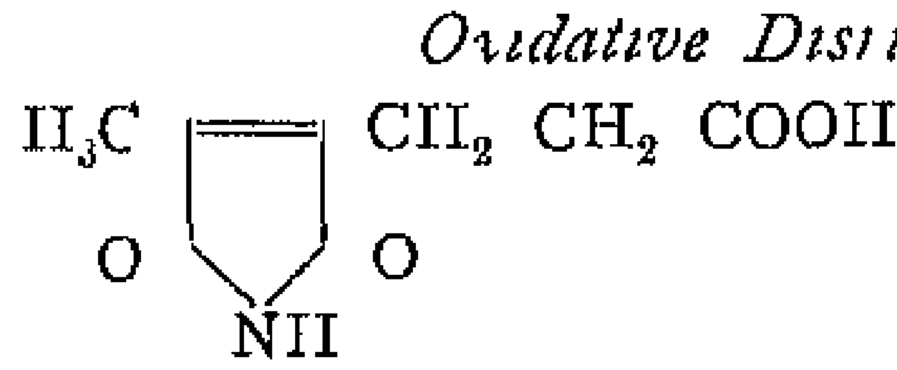


9 Xanthopyrrole carboxylic acid (?)

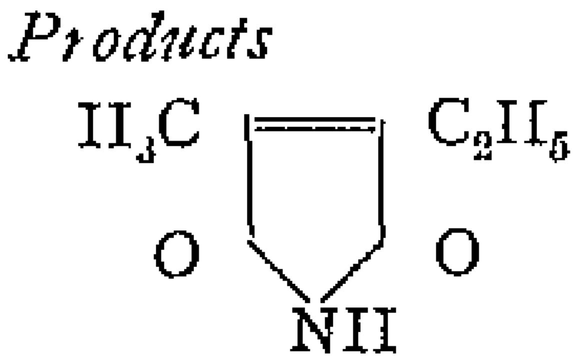
Good yields of alkylated decomposition products are obtained from hæmin by heating it under pressure at 230° with alcoholates, especially potassium methoxide The latter reagent leads exclusively to the formation of phyllopyrrole and phyllopyrrole carboxylic acid, thus confirming the above results[1]

Another valuable process is the *oxidation of hæmin and crude hæmopyrrole* first carried out by Kuster[2] The oxidative disruption of porphyrins in general has given much information concerning their structure

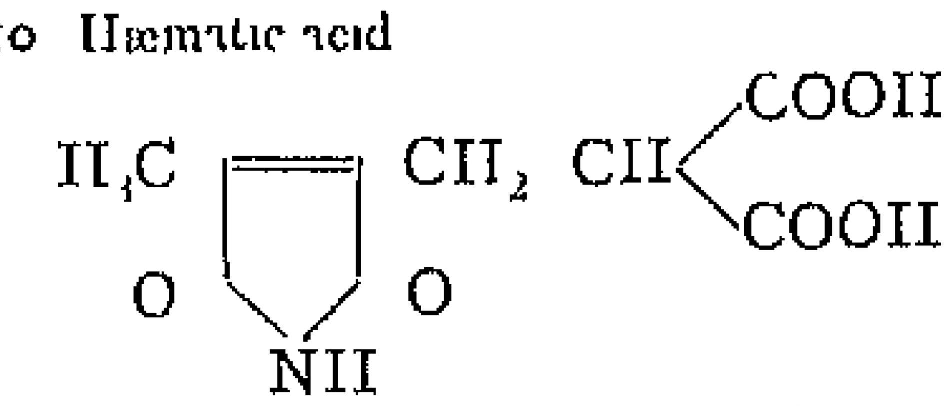
Oxidative Disruption Products



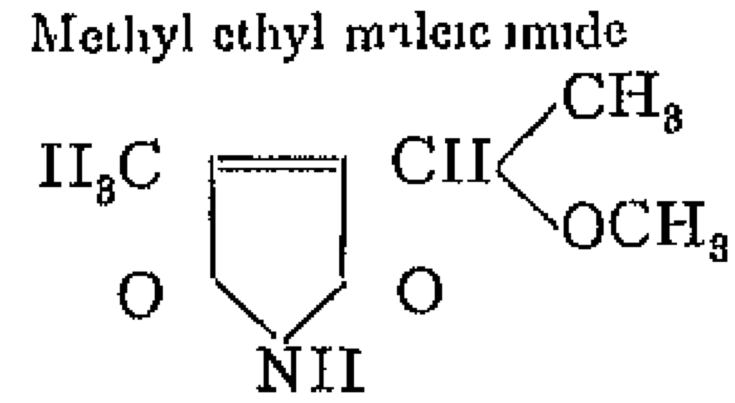
10 Hæmatic acid



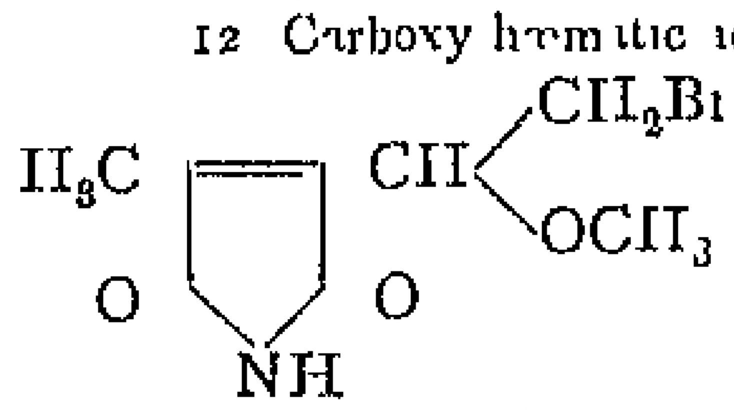
11 Methyl ethyl maleic imide



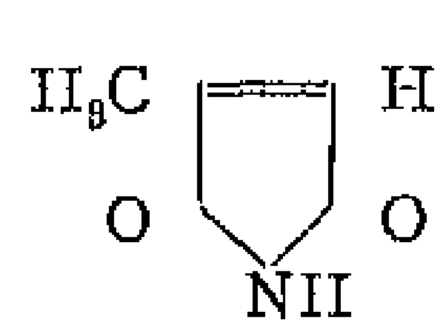
12 Carboxy hæmatic acid



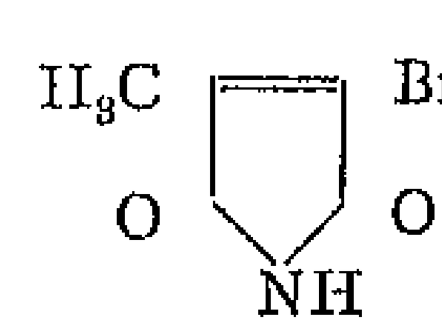
13 Imide m p 64



14 Imide, m p 75°



15 Citraconimide



16 Bromocitraconimide

[1] H Fischer and Rose, *Zeit physiol Chem*, 1913, 87, 39 [2] W Küster, *Ber*, 1902, 35, 2948, 1907, 40, 2017

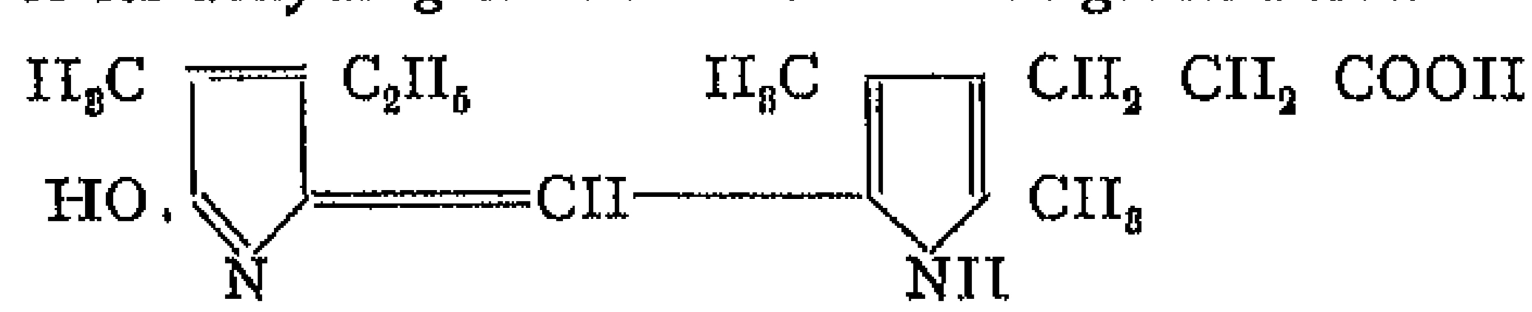
Kuster isolated **hæmatic acid** by oxidation of the colouring matters of blood and bile, and it has in addition been obtained from many porphyrins The oxidative conversion of these compounds into hæmatic acid (10) and similar derivatives has not only proved of great value in determining their constitution, but also led to a more systematic examination of the products of reductive disruption (p. 572) and to the isolation of pyrrole-carboxylic acids from this source Hæmatic acid has been synthesised by Kuster[1] from acetoacetic ester

A further oxidation product is the carboxylated hæmatic acid formulated provisionally as in 12 above, which on being heated to a high temperature yields hæmatic acid and methyl-ethyl-maleinimide It is obtained by oxidation of *uroporphyrin* and its synthetic analogue iso-uroporphyrin[2]

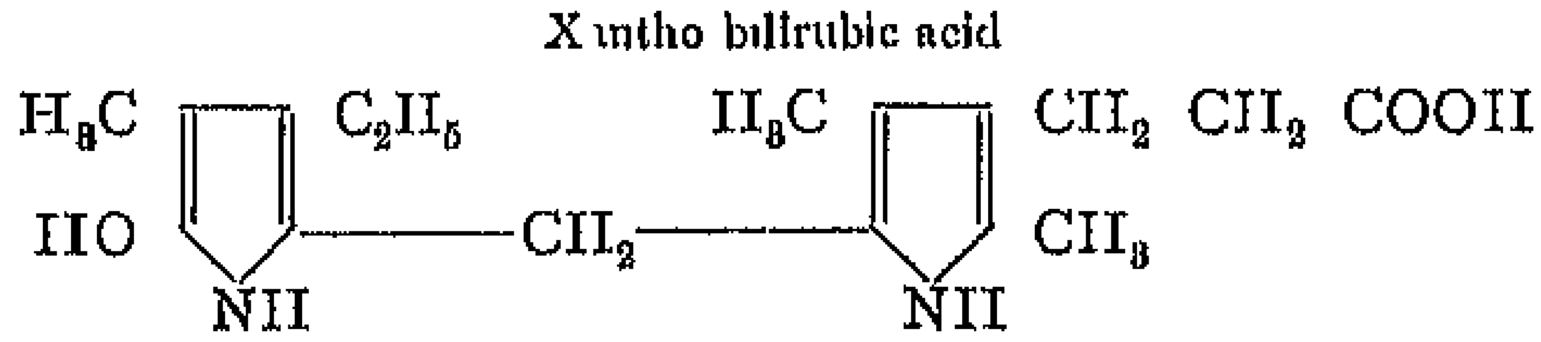
Among other important disruption products are the methoxy- and bromo-methoxy imides 13 and 14, both isolated by Kuster[3] by oxidation of tetramethyl-hæmatoporphyrin dimethyl ether The structure of these compounds has not yet been fully confirmed

Finally citraconimide and bromocitraconimide (16) may be mentioned, these were obtained with hæmatic acid from deuteroporphyrin,[4] dibromodeuteroporphyrin and bromoporphyrin[5]

Dipyrrole degradation products of hæmin and of porphyrins are not yet known, although **bilirubic acid** was discovered almost at the same time by Piloty[6] and H Fischer[7] among the reduction products of the colouring matter of bile The constitution of this compound together with that of its dehydrogenated derivative are given below



Xantho bilirubic acid



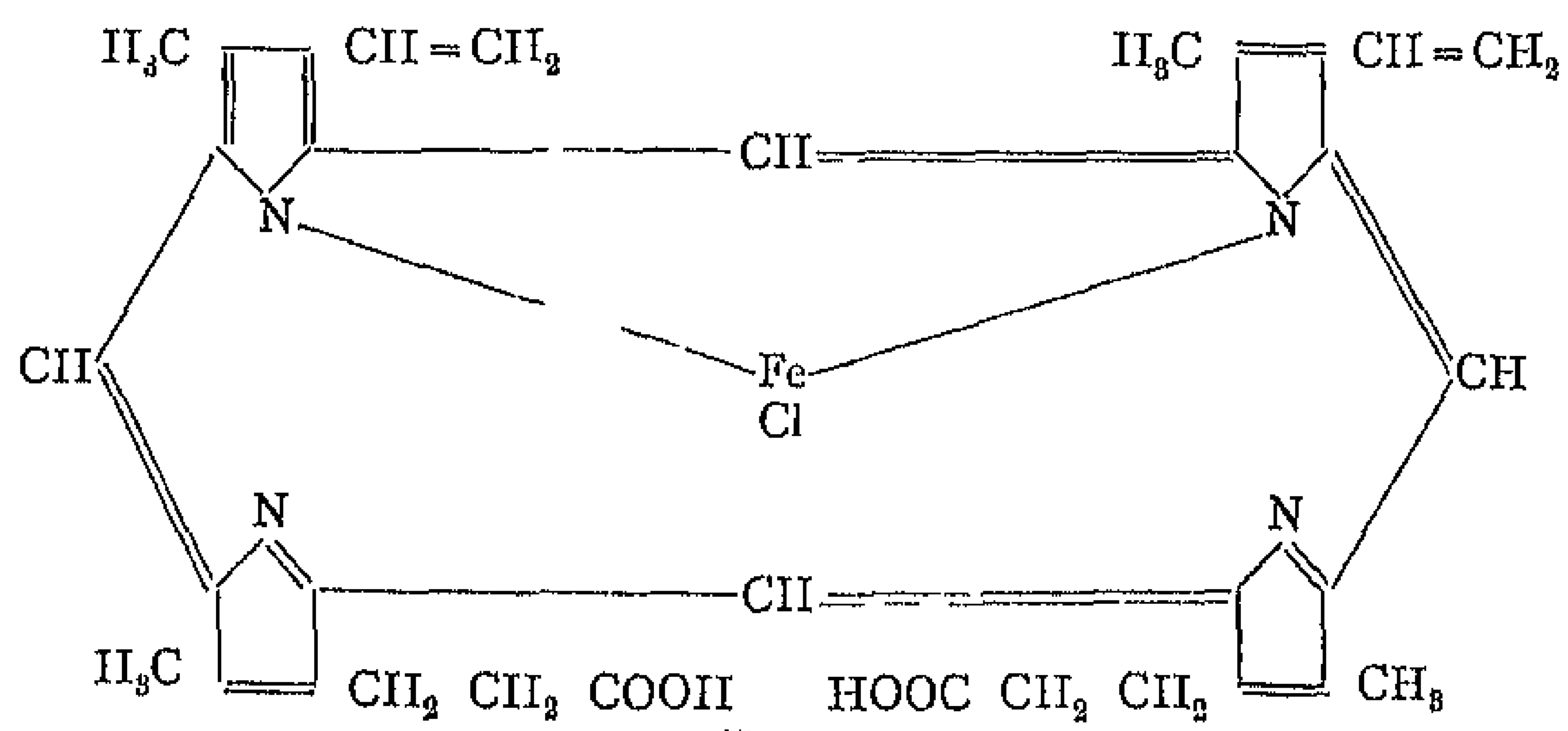
Bilirubic acid

The brown colouring matter of bile, *bilirubin*, $C_{33}H_{36}O_6N_4$, also resembles hæmin in yielding hæmatic acid on oxidation with chromic acid

A consideration of the disruption products described in the foregoing pages, shows that hæmin and the porphyrins must possess very complex molecular structures[8] From the experimental evidence

[1] Küster and Weller, *Ber*, 1914, 47, 532 [2] H Fischer and P Heisel, *Ann*, 1927, 457, 99. [3] W Küster, *Zeit physiol Chem*, 1927, 168, 270, 168, 295 [4] H Fischer and F Lindner, *Zeit physiol. Chem*, 1926, 161, 18 [5] H Fischer and F Kotter, *Ber*, 1927, 60, 1862 [6] Piloty and Thannhauser, *Ann*, 1912, 390, 191 [7] H Fischer and Röse, *Ber*, 1912, 45, 1579; *Zeit. physiol Chem*, 1914, 89, 255 [8] W Küster, *Zeit physiol Chem*, 1927, 168, 267.

Kuster deduced a formula for hæmin which was almost identical with the following of H. Fischer:



Hæmin

Final proof of the constitution rests upon the brilliant syntheses of H. Fischer,[1] which have resulted in the synthetic preparation of a great number of porphyrins, including *protoporphyrin* (the iron complex of which is hæmin), *hæmatoporphyrin* and *ætioporphyrin*.

Among porphyrins found in the organism may be mentioned *koproporphyrin*, $C_{36}H_{38}N_4O_8$, present in fæces and urine, and *uroporphyrin*, $C_{40}H_{38}N_4O_{16}$, in urine.

The formation of hæmopyrrole under the conditions described on p. 572 is not only of importance in connection with the constitution of the colouring matter of blood, but has also a direct bearing upon that of another natural colouring matter, **chlorophyll**.

Nencki and Marchlewski also obtained *hæmopyrrole* by reducing *phyllocyanin* (one of the parent compounds of phylloporphyrin, and closely related to chlorophyll) with hydriodic acid and phosphonium iodide. This reaction provides definite proof of the close relationship existing between the colouring matters of blood and of leaves. Willstätter and Asahina[2] later prepared hæmopyrrole from phylloporphyrin and other chlorophyll derivatives.

Degradation reactions similar to those carried out by Küster on hæmatin have also been applied by Marchlewski to phylloporphyrin.

The significance of this connection between chlorophyll and the colouring matter of blood lies in its indication of a kindred relationship between the vegetable and animal organism. The form of a living cell is regulated by its metabolism, and this in turn is dependent on its chemical nature. Hence the above resemblance between two substances of such different functions is of great importance for the correct understanding of the history of the development of the organism.

[1] H. Fischer and co-workers, *Ann.*, 448-468; especially 1929, 468, 98. [2] *Ann.*, 1911, 385, 188.

Pyrrole 2 aldehyde,[1] $C_4H_3(CHO)NH$, is formed by the interaction of pyrrole and chloroform in the presence of aqueous potassium hydroxide, thus providing a further illustration of the similarity between pyrrole and the phenols (see p 567)

$$C_4H_5N + CHCl_3 + 3KOH = C_4H_4N(CHO) + 3KCl + 2H_2O$$

It crystallises from cooled petroleum ether in colourless odourless prisms, m p 45°, and shows no resemblance to benzaldehyde

Other representatives of this difficultly accessible class have been prepared by H Fischer, the aldehyde group being introduced into the pyrrole nucleus by Gattermann's method, using anhydrous hydrogen cyanide and dry hydrogen chloride in absolute ethereal solution

Pyrrole Carboxylic Acids—A large proportion of the pyrrole derivatives known at present are carboxylic acids The simple pyrrole carboxylic acids resemble phenol carboxylic acids and are formed by similar reactions, *e g* —

1 By the oxidation of homologues of pyrrole by fusion with potash

2 By treating potassium pyrroles with carbon dioxide,

$$C_4H_4NK + CO_2 = C_4H_3(COOK)NH$$

3 From pyrroles by interaction with carbon tetrachloride and alcoholic potash

Esters of homologous pyrrole carboxylic acids can be obtained according to the methods given on p 564 When heated, the carboxylic acids readily part with carbon dioxide and yield the corresponding pyrrole

Since pyrrolidine-α-carboxylic acid has been identified as a disruption product of proteins,[2] and other pyrrolidine carboxylic acids have been discovered in tropinic acid and hygrinic acid, which are degradation products of alkaloids, a number of attempts have been made to prepare these acids by hydrogenating the corresponding pyrrole carboxylic acids or esters So far, however, no satisfactory method of effecting this change has been discovered

2 Hydropyrrole Derivatives

Hydropyrrole derivatives (see Pyrroline and Pyrrolidine, p 563) are obtained partly by direct hydrogenation of pyrrole derivatives, partly by the degradation of alkaloids, and partly by synthesis from aliphatic compounds In addition, certain tetra-hydro-pyrrole bases may be prepared from piperidines by a series of reactions to be described later, which involve the transformation of a six- into a five-membered ring The reduction of pyrrole compounds to di- and especially to tetra-hydro-derivatives offers considerable experimental difficulty, in this respect these compounds differ from the pyridine group

Addition of hydrogen brings about a decided change in chemical

[1] E Bamberger and Djierdjian, *Ber*, 1900, 33, 536 [2] E Fischer, *Z physiol Ch*, 1901, 33, 151, 412.

nature Whereas pyrrole itself is quite a weak base, pyrroline and to a still higher degree pyrrolidine possesses the strong basic properties of the secondary aliphatic amines This is the usual consequence of hydrogenating an aromatic system, as has already been seen in the case of the naphthylamines and will be observed again in the pyridine group

Pyrroline is a very volatile colourless liquid, which boils at 90° (748 mm) and fumes in air It readily abstracts moisture from the air and is therefore difficult to obtain free from traces of water

The Pyrrolidines

Pyrrolidine and its derivatives present a striking resemblance to the corresponding compounds of the piperidine series This similarity extends even to physical properties and is best illustrated by comparison with the analogy existing between compounds of the pentamethylene and hexamethylene groups

The discovery of pyrrolidine in 1885 was followed immediately by the recognition of its resemblance to piperidine and its description as a nuclear homologue of the latter (Ciamician)

The term nuclear or **ring homology**, which was originally used only to describe the relationship of the free parent bases, can in the state of our present knowledge be extended compound by compound to the corresponding members of the pyrrolidine and piperidine series In this manner the similarity is found to hold true for all the more important types of derivatives

Pyrrolidine, *tetrahydro-pyrrole, tetramethylene-imine*, C_4H_8NH, may be obtained by the following methods —

1 It was first prepared[1] by heating pyrrole with hydriodic acid and phosphonium iodide at 240° to 250° Obviously the less hydrogenated compound pyrroline must be formed as an intermediate product, and this can also be used as starting material

2 By the reduction of ethylene cyanide Ladenburg obtained pyrrolidine together with tetramethylene diamine (I) It is also produced by distilling the hydrochloride of tetramethylene diamine

3 A similar mode of preparation was discovered by Gabriel[2] in the interaction of δ-chloro butylamine (II) and sodium hydroxide

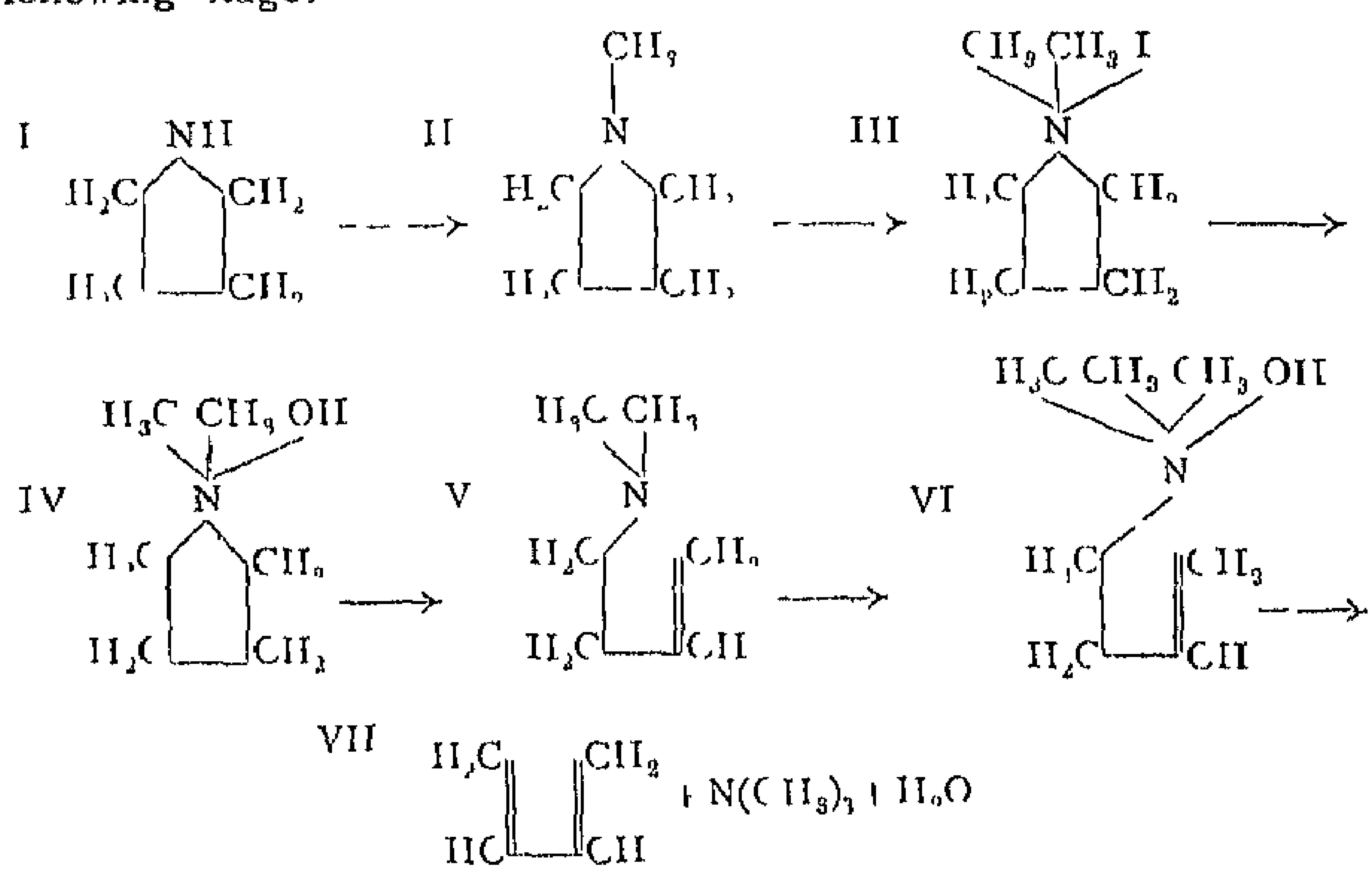
$$\begin{array}{lll} \text{I} & H_2N\,CH_2\,CH_2\,CH_2\,CH_2\,NH_2 & \xrightarrow{-NH_3} \\ & & \qquad \begin{array}{l} H_2C{-}CH_2 \\ \;\;| \\ H_2C{-}CH_2 \end{array}\!\!>NH \\ \text{II} & Cl\,CH_2\,CH_2\,CH_2\,CH_2\,NH_2 & \xrightarrow[-HCl]{} \end{array}$$

Despite the variety of preparative methods available, pyrrolidine is a difficultly accessible compound It is a strongly alkaline liquid of

[1] Ciamician and Magnaghi, *Ber*, 1885, 18, 2079 More recently the reduction has been effected by means of nickel as catalyst by the method of Sabatier and Senderens (Padoa, *C*, 1906, I, 1436) [2] *Ber*, 1891, 24, 3233 *Cf* also Schlinck, *Ber*, 1899, 32, 947

boiling-point 86° to 88°; it is miscible with water and possesses a pungent ammoniacal smell recalling that of piperidine. In general it shows great similarity to piperidine.

Behaviour of Pyrrolidine on Exhaustive Methylation.—If dimethyl-pyrrolidinium iodide (III.) be heated with caustic potash, a decomposition ensues resembling that described later under dimethyl-piperidinium hydroxide. Under these conditions the ring opens[1] with formation of an unsaturated aliphatic base, Δ^3-butenyl-dimethylamine (V.), (incorrectly called dimethyl pyrrolidine). The methiodide of this base, on distillation with alkali, yields trimethylamine and an unsaturated aliphatic hydrocarbon known as pyrrolylene or divinyl (VII.). The exhaustive methylation of pyrrolidine may be represented in the following stages[2]:—

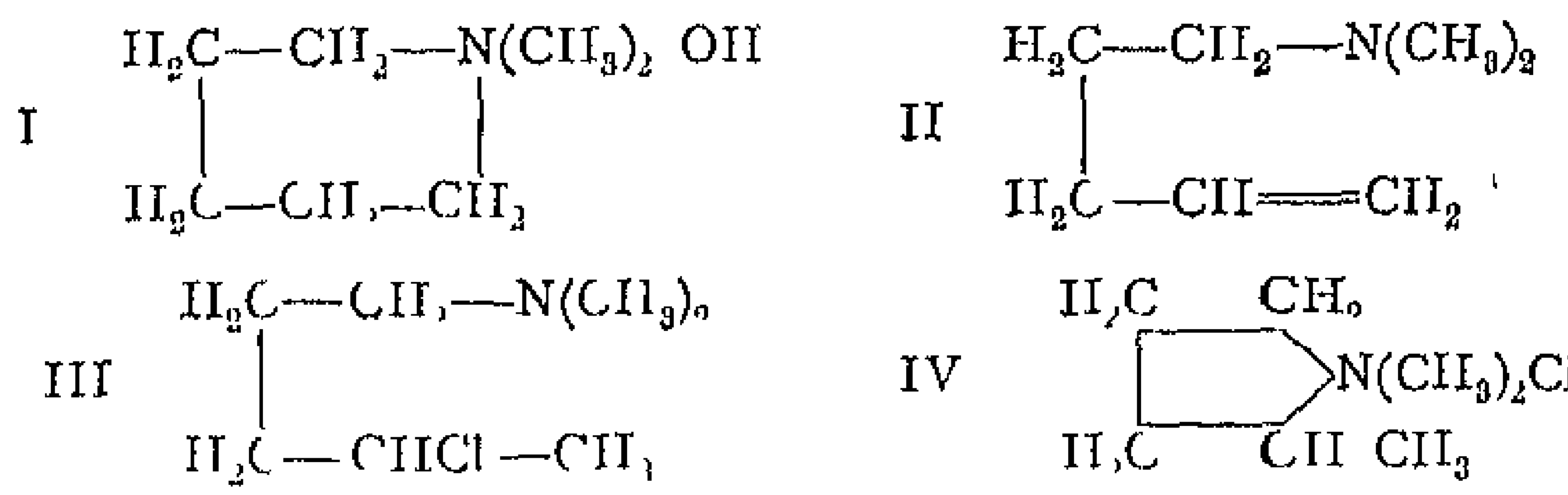


Homologues of Pyrrolidine.—The preparative methods described under pyrrolidine are also available for the formation of its homologues (see p. 577). In addition, a reaction has been discovered by Merling,[3] by means of which *the six-membered piperidine ring can be converted into the five-membered ring of pyrrolidine.*

Piperidine, or pentamethylene-imine, unites with methyl iodide to form dimethyl-piperidinium iodide, the hydroxide of which

[1] Detailed information as to the behaviour of the different cyclic bases on "exhaustive methylation" will be found in a monograph by J. Schmidt, *Ueber die Halogenalkylate und quaternären Ammoniumbasen* (Enke, Stuttgart, 1899). [2] For the disruption of the pyrrolidine ring by the phosphorus halide method, see J. v. Braun, *Ber.*, 1906, 39, 4119. Investigation of the disruption by means of cyanogen bromide has led to the unexpected result that the pyrrolidine ring is much more readily opened than the piperidine ring; J. v. Braun, *Ber.*, 1911, 44, 1152. [3] *Ann.*, 1891, 264, 310; 1894, 278, 1.

(I) on distillation gives an open-chain compound (II) known as Δ^1-pentenyl-dimethylamine (sometimes incorrectly called dimethyl-piperidine) The addition product (III) formed by the latter with hydrochloric acid easily isomerises into the methochloride of 1 2-dimethyl-pyrrolidine (IV), which on stronger heating breaks up into methyl chloride and 1 2-dimethyl-pyrrolidine



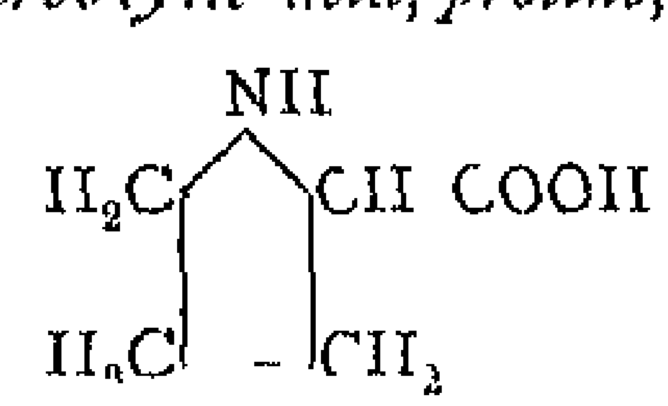
Just as pyrrolidine on exhaustive methylation gives the unsaturated hydrocarbon divinyl, CH_2 CH CH CH_2 (see p 578), 3-methyl-pyrrolidine gives β-methyl-divinyl, CH_2 CH $C(CH_3)$ CH_2, which is more commonly known as isoprene[1]

Pyrrolidine Carboxylic Acids

Certain important degradation products of the *coca* and *atropa* alkaloids have been identified as carboxylic acids of pyrrolidine, viz, hygrinic acid and tropinic acid Further, it has been shown by E Fischer that pyrrolidine-2-carboxylic acid occurs as a hydrolysis product of casein, egg albumin, blood fibrin and other albuminous substances when they are treated with hydrochloric acid

As a result of the above discoveries the pyrrolidine carboxylic acids, which had previously been little examined, were investigated in greater detail For general methods of synthesising these compounds reference should be made to p 565 The application of the methods to special cases is described below

Pyrrolidine 2 carboxylic acid, *a-pyrrolidine carboxylic acid, proline,* was first isolated in an optically impure *l*-form by E Fischer, from the mixture obtained by hydrolysing casein with hydrochloric acid It has since been obtained from a number of other proteins[2]



Hence it must be assumed that pyrrolidine-2-carboxylic acid is a primary product of the hydrolysis of proteins, and that it is an important unit of the protein molecule

[1] W Euler, C, 1898, I, 217 [2] E Fischer and co workers, *Z physiol Ch*, 1901, 33, 151, 412, 35, 70, 227, 36, 268, 462, 39, 81, 40, 215 Ssalaskin and Kowalewsky, *ibid*, 1903, 38, 567 Kossel, *ibid*, 1904, 40, 311 Abderhalden, *ibid*, 1904, 41, 55, 44, 17, 276, 46, 24, 31 C Neuberg, C, 1904, II, 1576.

Syntheses of Pyrrolidine-2-carboxylic Acid.—1. The synthesis of Willstätter and Ettlinger[1] is an adaptation of the general procedure described under 5, p. 565, and is carried out as follows:—

Molecular quantities of trimethylene bromide and sodio-malonic ester interact under certain conditions to give bromo-propyl-malonic ester, according to the equation

$$CHNa(COOC_2H_5)_2 + CH_2Br \cdot CH_2 \cdot CH_2Br$$
$$= NaBr + CH_2Br \cdot CH_2 \cdot CH_2 \cdot CH(COOC_2H_5)_2$$

This, when treated with bromine, yields $\alpha\delta$-dibromo-propyl-malonic ester, which can be condensed with ammonia to form the diamide of pyrrolidine-2-dicarboxylic acid. On heating with hydrochloric acid the latter is smoothly converted into pyrrolidine-2-carboxylic acid.

2. Fischer has prepared the compound in a similar manner by the interaction of ammonia and phthalimido-propyl bromomalonic ester,

$$C_6H_4\langle{}^{CO}_{CO}\rangle N \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CBr(CO_2C_2H_5)_2$$

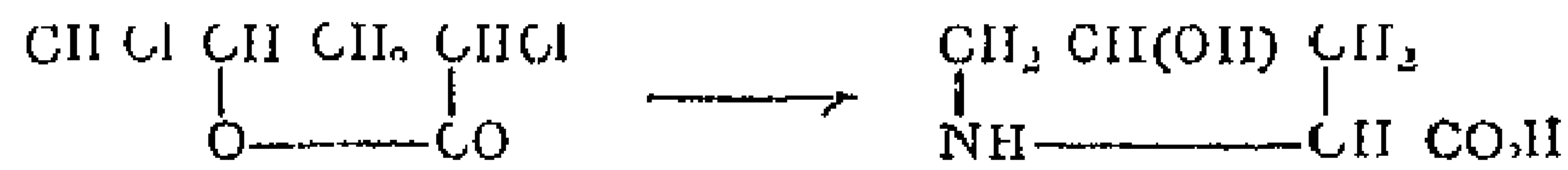
3. According to Putochin[2] proline may be prepared by the direct action of trimethylene bromide on amino-malonic ester, $NH_2 \cdot CH(COOC_2H_5)_2$. Naturally these syntheses yield the acid in the racemic form.

After careful drying, dl-*pyrrolidine-2-carboxylic acid* melts with gas evolution at 205°. In aqueous solution it gives a weakly acid reaction with litmus, and possesses a sweet taste. For the separation and identification of the acid the *copper salt*[3] is of service, and has frequently been used by Fischer for identifying the compound obtained from proteins. If the acid be saturated with precipitated copper hydroxide, a dark blue solution is obtained from which the copper salt ($2H_2O$) deposits in deep blue four-sided plates. The salt dissolves readily in hot water, but only sparingly in the cold. It is slightly soluble in alcohol and insoluble in chloroform.

l-*Pyrrolidine-2-carboxylic acid* forms flat needles, melting at 205°. Rotation in aqueous solution $[\alpha]_D^{20} = -71.94$ to $-77.40°$, in hydrochloric acid solution $[\alpha]_D^{20} = -46.53°$, and in alkaline solution $[\alpha]_D^{20} = -83.48°$. On being heated for five hours with baryta at 140° to 145°, it is converted into the racemic form.

[1] Willstätter and Ettlinger, *Ber.*, 1900, 33, 1160; *Ann.*, 1903, 326, 91. [2] N. J. Putochin, *Ber.*, 1923, 56, 2213. [3] *Ann.*, 1903, 326, 105; *Ber.*, 1901, 34, 459.

β'-Hydroxy-pyrrolidine-α-carboxylic acid, *hydroxy-proline*, has been identified by E. Fischer among the hydrolysis products of gelatin and synthesised by Leuchs[1] in its various stereoisomeric forms by the action of ammonia on αδ-dichloro-valerolactone.



Tropinic acid, 1-methyl-pyrrolidine-2-carboxy-5-acetic acid,

When tropine and ecgonine (see chapter on Alkaloids) are oxidised with chromic acid[2] they yield dicarboxylic compounds, $C_8H_{13}NO_4$, known as tropinic acids. These differ only in their optical properties, the oxidation product from tropine being inactive, and that from ecgonine dextrorotatory.

The constitution of tropinic acid has been established by Willstätter in the following way:

1. Tropinic acid derived from various sources was submitted to exhaustive methylation, and in every case the same product of composition, $C_5H_6(COOH)_2$, was obtained, which from its behaviour with bromine was shown to be a diolefinic dicarboxylic acid. This acid, on being reduced in alkaline solution with sodium amalgam, gave a partly reduced acid together with a saturated acid identified as normal pimelic acid.[3] These facts taken in conjunction with certain reactions of tropinone (see this) were sufficient to establish the constitution of tropinic acid.

2. By treating tropinic acid (or better, ecgoninic acid) with chromic acid mixture, Willstätter obtained methyl-succinimide. The pyrrolidine nucleus of this acid, and therefore of tropine and ecgonine, has thus been isolated in the form of a simple well-known compound.

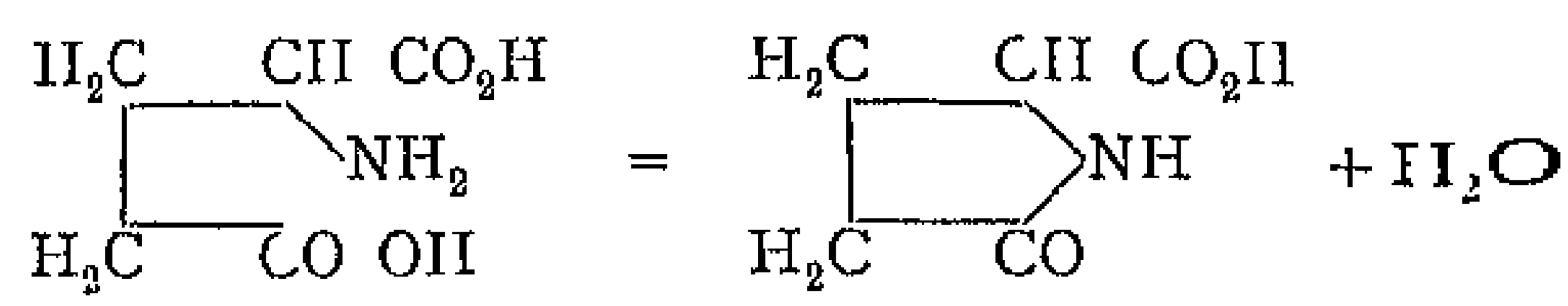
Racemic tropinic acid is very soluble in water, difficultly soluble in alcohol, and insoluble in benzene and ether. It melts indefinitely with decomposition at about 250°. d-*Tropinic acid*, obtained by the oxidation of either *l*- or *d*-ecgonine, melts at 253°, $[\alpha]_D = +14.8°$ in water.

Carboxylic Acids of 2-Ketopyrrolidine (α-Pyrrolidone)

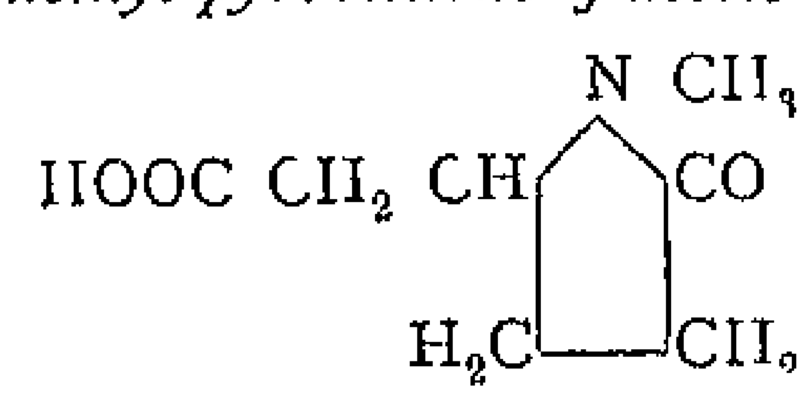
The acids of chief interest in this group are pyrrolidone-5-carboxylic acid, a hydrolysis product of proteins, and ecgoninic acid (1-methyl-pyrrolidone-5-acetic acid) which is an oxidation product of tropine and ecgonine.

[1] H. Leuchs and Bormann, *Ber.*, 1919, 52, 2086. [2] C. Liebermann, *Ber.*, 1890, 23, 2518; 1891, 24, 606. For the preparation of tropinic acid from tropine and ecgonine, compare also Willstätter, *Ber.*, 1895, 28, 3278 (footnote); *Ber.*, 1898, 31, 1547. [3] *Ber.*, 1898, 31, 1534.

Pyrrolidone-5-carboxylic acid, 2-ketopyrrolidine-5-carboxylic acid, $C_4H_6O(COOH)NH$, was first obtained by heating optically active glutamic acid (α-amino-glutaric acid) at 180° to 190°, and was therefore described under the name of pyroglutamic acid. The same acid has also been obtained by heating protein with baryta at 180°. Subsequently it was prepared from inactive glutamic acid, of which it is the lactam, and investigated in greater detail.[1]

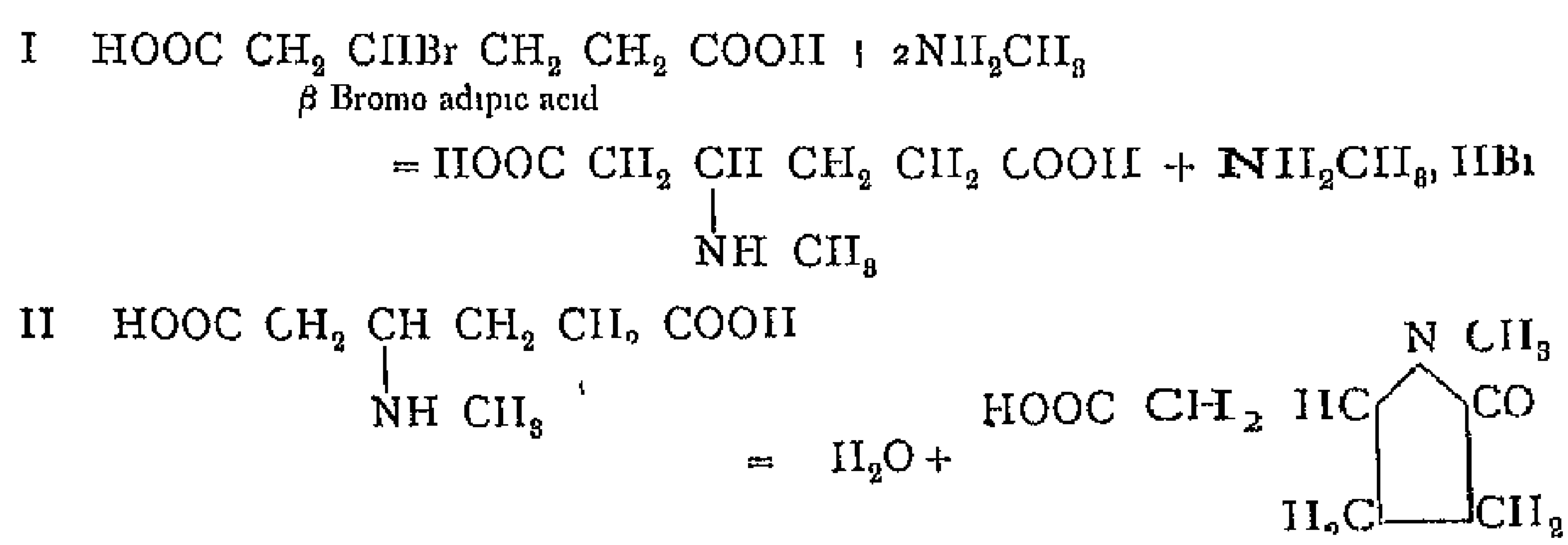


Ecgoninic acid, 1-*methyl-pyrrolidone-5-acetic acid*



It has already been stated (p. 581) that the oxidation of tropine or ecgonine with chromic acid yields tropinic acid. In addition, Liebermann observed that two modifications of ecgoninic acid were produced as by-products in this reaction; *l*- and *d*-ecgonines were found to give a laevorotatory acid, m.p. 117°, while tropine gave an acid of doubtful purity, melting about 90°. Later it was shown by Willstätter[2] that the ecgoninic acid from tropine is the racemic form, whereas that from ecgonine is the *l*-variety.[3] The acids are alike in all important properties, but differ in melting-point (*r*-form melts at 93° to 94°) and to some extent in solubility. The above constitution has been confirmed by Willstätter's synthesis of the racemic acid, which was effected in the following manner:—

Δ^2-*Dihydro-muconic acid*, which has been synthesised from glyoxal and malonic acid, combines with HBr to form β-bromo-adipic acid. In methyl alcoholic or benzene solution this readily reacts with



[1] L. Wolff, *Ann.*, 1890, 260, 124. [2] Willstätter and Bode, *Ber.*, 1901, 34, 519. [3] The degradation of tropine and ecgonine to ecgoninic acid, in which tropinic acid is probably an intermediate stage, is dealt with in more detail in connection with the vegetable alkaloids.

methylamine to give ecgoninic acid, probably through the intermediate formation of methylamino adipic acid

The synthetic product is identical in all respects with that obtained by the oxidation of tropine This synthesis provided the first direct proof of the existence of a pyrrolidine ring in atropine and cocaine

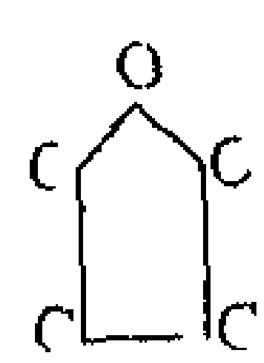
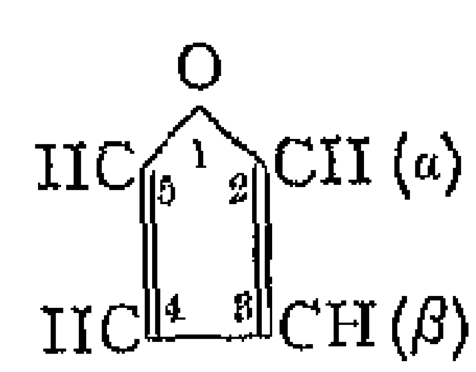
r-Ecgoninic acid crystallises in white needles, m p 93° to 94° It is readily soluble in water, alcohol and chloroform, dissolves very sparingly in boiling benzene and is practically insoluble in ether or ligroin It has no physiological action The pyrrolidone ring in this compound is so stable that it has not yet been found possible to convert the acid into the open chain β methylamino adipic acid

l-Ecgoninic acid[1] can be obtained, as mentioned above, from *l* or *r* ecgonine It melts at 117° to 118°, and is less soluble than the *r* acid

The alkaloids of the pyrrolidine group are treated in a later chapter

II —FURFURANE GROUP

Furfurane, as indicated on p 248, is closely related to pyrrole, but is of much less importance than the latter It contains a ring composed of four carbon atoms and one oxygen atom (I),

I  II 

which may be regarded as a pyrrole ring in which the NH group is replaced by O

The synthetic formation of furfurane derivatives by elimination of water from γ-diketo-compounds has already been described (see pp 248 and 251), and affords a good illustration of the close relationship existing between furfurane and pyrrole

Furane or **furfurane**, C_4H_4O (formula II), can be obtained from mucic acid (*cf* p 566) On dry distillation the latter is converted into *pyromucic* or *furane-carboxylic acid*, which on heating in a sealed tube at 270° yields furane

$$\underset{\text{Mucic acid}}{C_4H_4(OH)_4(COOH)_2} \longrightarrow \underset{\text{Pyromucic acid}}{C_4H_3O(COOH)} \longrightarrow \underset{\text{Furane}}{C_4H_4O + CO_2}$$

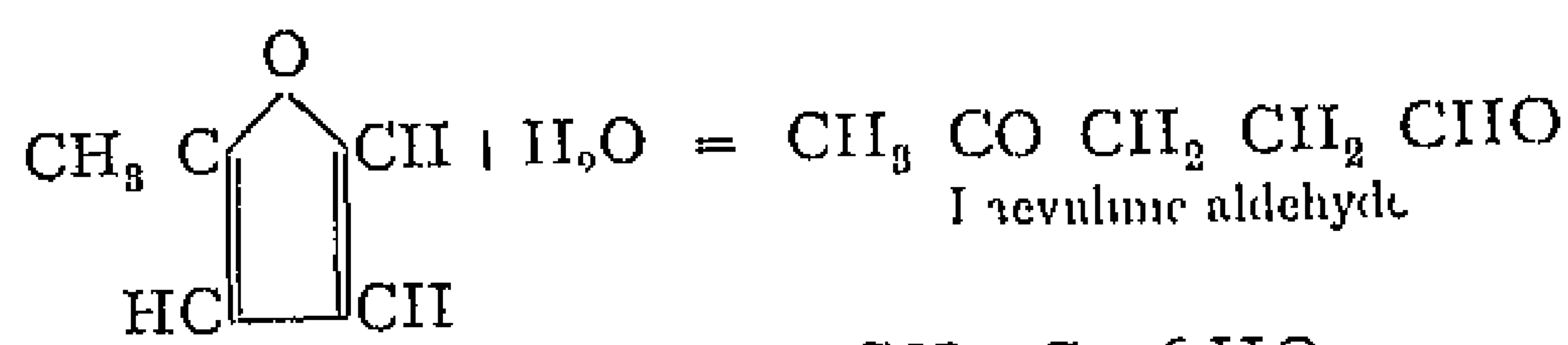
It is a colourless liquid with a peculiar smell resembling that of chloroform Furane boils at 32° and is insoluble in water The vapour gives a green coloration to a pine splint moistened with hydrochloric acid

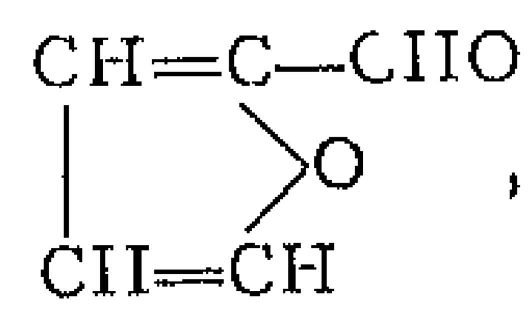
The position of substituents in the furane nucleus is indicated, as in the case of pyrrole, by letters or numbers (formula II)

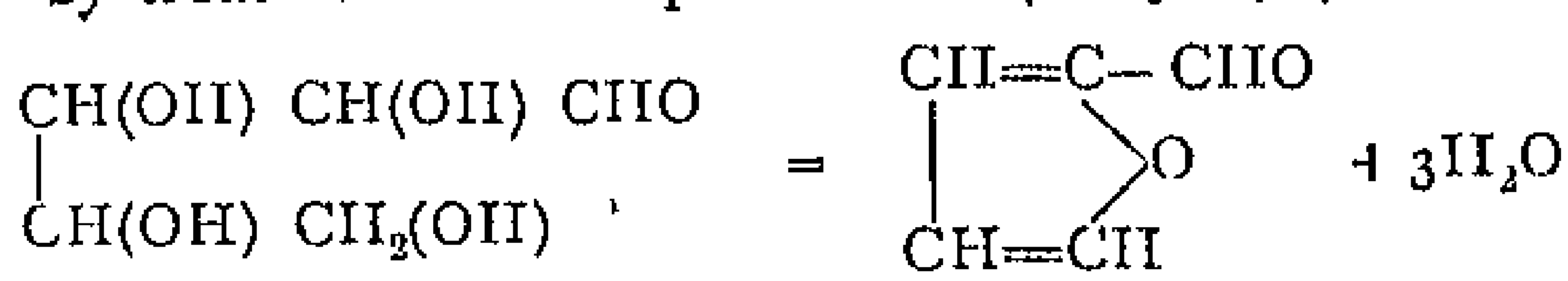
α-Methyl-furane, sylvane, is contained in the volatile portion of the tarry oil from *Pinus sylvestris*, in which dimethyl-furane and

[1] Willstätter and co workers, *Ber*, 1901, 34, 522, *Ann*, 1903, 326, 90

higher methylated products are also present, it can be isolated from the fraction of beech tar creosote[1] boiling between 60° and 70° It boils at 65° and is a colourless mobile liquid of pleasant ethereal smell It gives an emerald green coloration to a pine splint moistened with concentrated hydrochloric acid On hydrolysis with hydrochloric acid[1] it yields laevulinic aldehyde



Furaldehyde, *furfural, furfurole,*  , has been known for a long time It is formed by the distillation of bran, wood or various carbohydrates with sulphuric acid, but is best prepared from arabinose or xylose—or from corn-cob gum,[2] which is rich in pentoses—by treatment with sulphuric acid (see p 295)



It boils at 162°, and is a colourless oil of pleasant smell

In its chemical character furfural is aromatic in type and a complete analogue of benzaldehyde Like all aldehydes it forms an oxime and a hydrazone, and in addition undergoes a series of reactions in which the resemblance to benzaldehyde is clearly visible

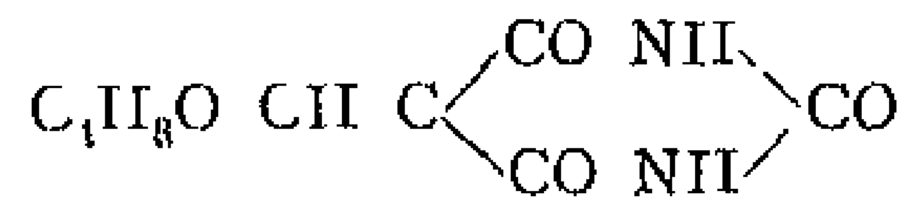
In an attempt to discover some technical use for the large quantities of furfural produced as a by-product in industry, its behaviour towards phenolic compounds has been examined[3] As in the case of formaldehyde, it is found that condensation takes place, particularly in the presence of suitable catalysts, with the elimination of water and the production of brownish-black substances These possess the properties of resins, and in most respects resemble the "Bakelites" produced by condensing formaldehyde with phenols (p 176) Furfural is used in the preparation of artificial resins, dyes and insecticides

As already mentioned, the conversion of pentoses into furfural is employed in determining the proportion of pentoses or pentosans present in various mixtures In this connection a number of insoluble derivatives have been found by means of which furfural may be separated from solution, *e g* furfural phloroglucide, probably formed according to the equation

$$C_6H_6O_3 + C_5H_4O_2 = C_{11}H_8O_4 + H_2O$$

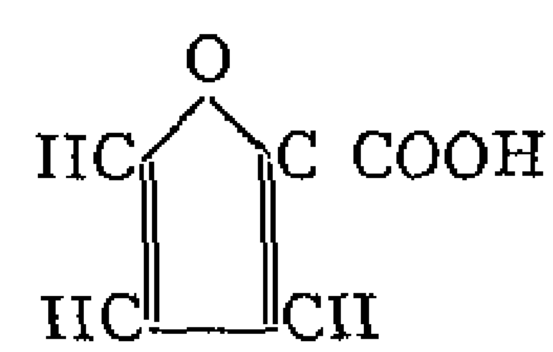
[1] C Harries, *Ber*, 1897, 30, 230 [2] K P Monroe, *J Ind and Eng Ch*, 1921, 13, 133
[3] E Beckmann and Dehn, *Ch Zeit*, 1919, I, 440

and the condensation product of furfural and barbituric acid, which is a very insoluble powder of the formula



A qualitative test for furfural is the formation of an intensely red dye-stuff when it is heated with aniline and hydrochloric acid.

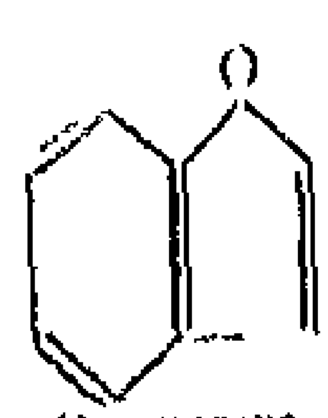
Pyromucic acid, α-furane-carboxylic acid, is formed, as described above, during the dry distillation of mucic acid, and also by the oxidation of furfural. It crystallises in needles, m.p. 134°, which sublime at 100° and dissolve readily in hot water or alcohol.[1]



From the properties of furfural it would be expected that pyromucic acid would behave as an aromatic acid and as the analogue of benzoic acid. This, however, is not the case. The reactions of pyromucic acid give no indication of aromatic character, but rather place it with the unsaturated aliphatic acids. Thus it immediately decolorises an alkaline solution of permanganate of potash, and when exposed to bromine vapour takes up four atoms of bromine. On warming with bromine water it is converted into fumaric acid, and on catalytic hydrogenation yields *tetrahydro-pyromucic acid* (m.p. 21°, b.p. 131°/14 mm.).

Another acid of this series is *furane 2: 4-dicarboxylic acid*, m.p. 266°. The formation of this substance by heating bromocoumalinic ester with potassium hydroxide is of interest as representing the transformation of a six- into a five-membered ring.[2]

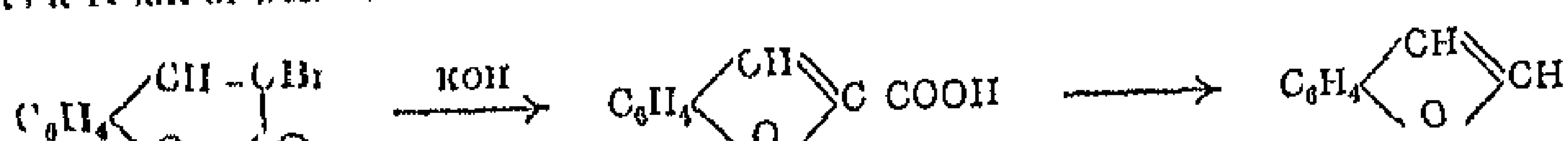
Coumarone or Benzofurane Series



Coumarone

Compounds of this class contain a benzene and a furane nucleus condensed together with two carbon atoms in common. The parent substance of the group, coumarone, thus bears the same relationship to naphthalene as furane to benzene. To furane it is related in the same way as indole (see later) to pyrrole.

Coumarone derivatives take their name from their formation by the action of alcoholic potash on α-halogen-substituted coumarins, as a result of which a six-membered ring is converted into a five-membered ring.

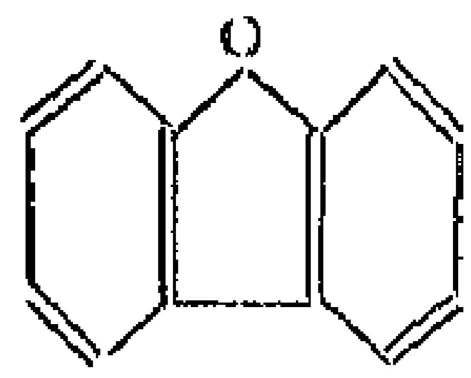


α Bromocoumarin — Coumarilic acid — Coumarone

Coumarone can be prepared by other methods[3] in addition to those described above, and is also found together with a number of methyl coumarones in coal tar. It boils at 169° to 170°, and is an extremely stable, indifferent compound. Strong mineral acids bring about resinification and formation of a polymeride.

[1] *Ann.*, 261, 379. [2] F. Feist, *Ber.*, 1901, 34, 1992. [3] *Cf.* R. Stoermer, *Ber.*, 1897, 30, 1700, 1711; *Ann.*, 1900, 312, 237; 313, 79; P. Karrer and co-workers, *Helv. Chim. Acta*, 1920, 3, 541; 1921, 4, 718.

known as *paracoumarone* On leading a mixture of coumarone and benzene or naphthalene in the vaporous state through a heated tube, phenanthrene and chrysene (see p 559) are formed



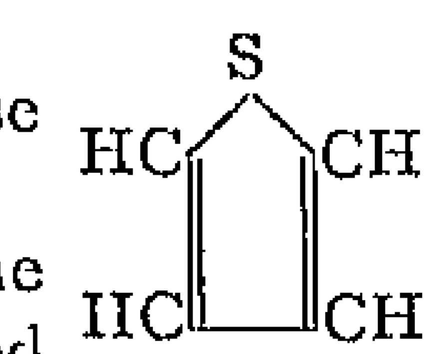
Diphenylene oxide

With chlorine and bromine coumarone yields dihalogen addition products, which, on being treated with alcoholic potash, give chloro and bromo coumarones Nitro derivatives are also known A large number of derivatives containing alkyl groups in the benzene and furane nuclei have been prepared by synthesis

Diphenylene oxide may be regarded as **dibenzo furane** It forms white leaflets, m p 81°, b p 288°, and is found in coal tar Synthetically it may be obtained by various methods, *e g* from phenol by distillation with lead oxide

III —THIOPHENE GROUP

Whereas pyrrole, as already emphasised, shows a strong resemblance to the phenols, thiophene possesses many points in common with benzene



This similarity extends also to derivatives of these compounds

Thiophene is present to about 0 5 per cent in the benzene obtained from coal tar, in which it was discovered in 1883 by Victor Meyer In addition it is found in the lower boiling fractions of the tar from brown coal Homologues of thiophene are present in the benzene homologues prepared from coal tar, thus the two possible (α and β) methyl-thiophenes or **thiotolenes**, $C_4H_3(CH_3)S$, are contained in commercial toluene, and the dimethyl-thiophenes or **thioxenes**, $C_4H_2(CH_3)_2S$, in xylol This is explained by the fact that corresponding homologues of the benzene and thiophene series possess approximately the same boiling-points Thiophene and its homologues may be isolated from the above aromatic hydrocarbons by taking advantage of the fact that they are more readily sulphonated than the latter on treatment with concentrated sulphuric acid

Many bituminous tars and oils, such as crude *ichthyol oil*, consist largely of *thiophene homologues* Propyl derivatives of thiophene have been isolated in comparatively large proportion from certain shale tar oils [1]

Synthetically, thiophene derivatives are formed in a similar way to those of pyrrole and furane from γ-diketo-compounds by treatment with phosphorus pentasulphide (see pp 248 and 251), and also by distilling succinic acid and its homologues with phosphorus pentasulphide [2]

Thiophene and its derivatives all give the *indophenine reaction*, *i e*, when treated with concentrated sulphuric acid and a little isatin, particularly in the presence of certain oxidising agents such as ferric chloride or nitric acid, a characteristic blue coloration is produced [3]

[1] H Scheibler and M Schmidt, *Ber*, 1921, 54, 139 [2] For a synthesis of thiophene derivatives from β-amino crotonic ester, see *Ber*, 1919, 52, 1605 [3] For the constitution of indophenin, see W Schlenk and O Blum, *Ann*, 1923, 433, 95

Thiophene can be extracted from commercial benzene by repeated shaking with small quantities of concentrated sulphuric acid, and decomposing the sulphonic acid so obtained by heating it strongly with water. This method of separation is by no means an ideal one, since either a certain proportion of benzene is simultaneously sulphonated, or, by using smaller amounts of sulphuric acid, the thiophene is only incompletely removed from the benzene.

A better and quantitative method of isolating thiophene from commercial benzene has been developed by O. Dimroth.[1] This consists in heating the mixture to the boiling-point with a solution of mercuric acetate, when thiophene is attacked with the formation of *thiophene dimercuri-hydroxyacetate*, $C_4H_2S(Hg \cdot O \cdot CO \cdot CH_3) \cdot HgOH$. The latter separates out, whereas the less reactive benzene is not attacked at this temperature. On distilling the mercury compound with moderately concentrated hydrochloric acid, it readily decomposes into mercuric chloride and thiophene. This method enables thiophene to be isolated in the pure state without loss of either thiophene or benzene. Thiophene may be synthesised by passing ethyl sulphide vapour through a red-hot tube, and by other pyrogenic reactions. In larger quantities it is obtained by heating sodium succinate with phosphorus trisulphide.

$$\begin{array}{l} CH_2-COONa \\ | \\ CH_2-COONa \end{array} \xrightarrow{P_2S_3} \begin{array}{l} CH=CH \\ | \qquad\quad \rangle S \\ CH=CH \end{array}$$

It possesses almost the same smell and boiling-point (84°) as benzene (80.4°), which it also closely resembles in its behaviour towards various reagents. Thus chloro- and bromo-substitution products of thiophene may be prepared by the direct action of halogens, in the same way as the corresponding benzene derivatives, although the reaction takes place more readily than with benzene. Mono- and dinitro-thiophenes are formed when air saturated with thiopene vapour is led through cooled fuming nitric acid. Mononitro-thiophene melts at 44°, boils at 224°, and has a smell resembling that of nitrobenzene. These nitro-compounds, however, are not reduced with the same ease as the nitrobenzenes, since the majority of reducing agents lead to their complete decomposition. The readiness with which thiophene is sulphonated has been mentioned above.

Homologues of thiophene are prepared from γ-diketones or alkyl succinic acids. They may also be obtained from thiophene by reactions analogous to those used in the preparation of benzene homologues from benzene, *e.g.* by Fittig's synthesis from sodium and a mixture of iodothiophene and an alkyl iodide, or from thiophene, alkyl bromide and aluminium chloride, and so on.

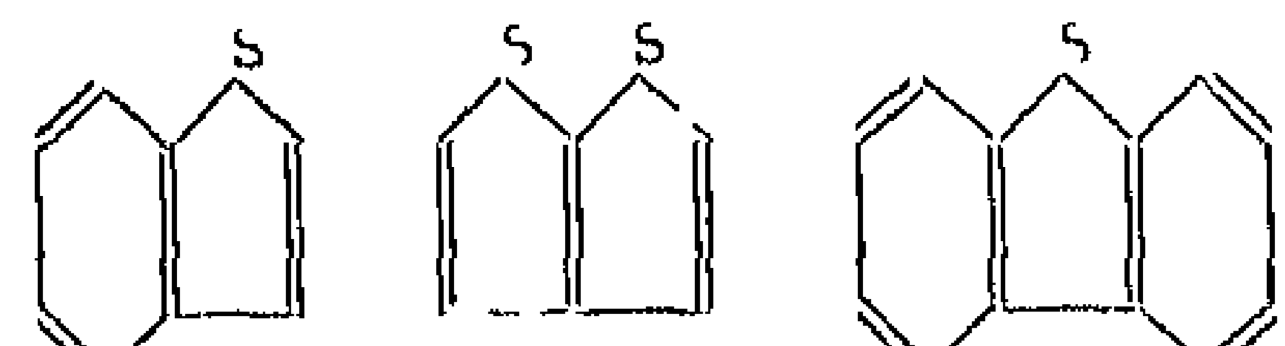
$$C_4H_3IS + CH_3I + 2Na = C_4H_3(CH_3)S + 2NaI$$

[1] *Ber.*, 1899, **32**, 759; 1902, **35**, 2035.

Thiophene aldehyde, $C_4H_3(CHO)S$, can be obtained by the action of hydrogen sulphide on chlorinated 1 2-diketo-pentamethylene In its properties it resembles benzaldehyde rather than furfural

Thiophene carboxylic acids are prepared in a similar manner to those of the benzene series by oxidising alkyl derivatives of thiophene, when the side chain is converted into a carboxyl group The α-acid can also be prepared by the action of sodium on a mixture of iodo-thiophene and chloro carbonic ester It resembles benzoic acid and crystallises from hot water in needles, m p 126 5°

Condensed thiophenes and benzo thiophenes are also known comparable to the corresponding benzene compounds, *e g*,



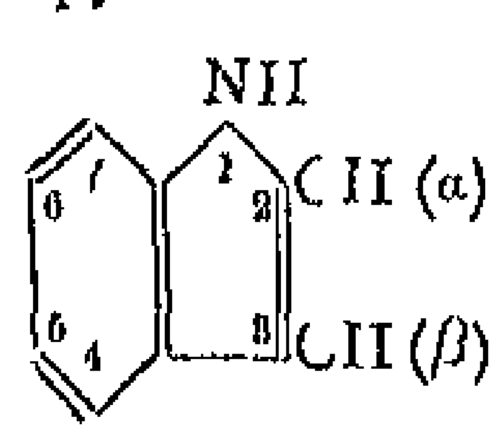
Thionaphthene   Thiophthene   Diphenylene sulphide

Thionaphthene[1] melts at 31, and boils at 221°, *i e*, at almost the same temperature as naphthalene (218°) It also resembles the latter in smell The true analogue of naphthalene in this series is **thiophthene**, which is formed by heating citric or tricarballylic acid with phosphorus sulphide, and is an oil of faint smell, b p 224° to 226 **Diphenylene sulphide**, a compound of anthracene type, is produced when diphenyl sulphide is led through a glowing tube It melts at 97° and boils at 332°

II

Benzopyrrole or Indole Group

The molecule of indole contains a benzene nucleus condensed with a pyrrole nucleus, as in the annexed formula As the parent substance of indigo it possesses an outstanding interest Indole and its derivatives are also important from the chemico physiological point of view, owing to their occurrence as disruption products of proteins Four compounds of this group have long been known to be present among the putrefaction products of proteins, namely, indole itself, skatole, skatole-carboxylic acid and tryptophane A valuable series of investigations on compounds of the indole group was carried out by Baeyer in connection with the constitution and synthesis of indigo The results obtained have contributed not only to our knowledge of indole derivatives, but also very largely to our progress in general organic chemistry Thus the theory of ring-formation gained considerably from the study of indole,



[1] For a synthesis see Gattermann and Lockhart, *Ber*, 1893, 26, 2808

and the theory of desmotropy from that of isatin. Further, the researches on indigo led to the discovery of a number of new methods which have since been applied with success to other branches of organic chemistry.

Indole, C_8H_7N, is produced in small amounts by the putrefaction of albuminous material, and is present in fæces; it is also formed by the alkaline hydrolysis of proteins.[1] It occurs in coal tar, and has been isolated from a fraction of tar oil,[2] boiling between 240° and 260°. Indole is also present in jasmine flower oil (2½ per cent), in orange blossom and other flowers. The structural formula quoted above was advanced by Baeyer before the compound itself had been discovered.

Indole is obtained by the following reactions:—

1. From its oxygenated derivatives such as indigo, oxindole or indoxyl by reduction. For example, by distilling oxindole with zinc dust:

$$\underset{\text{Oxindole}}{C_6H_4\left\langle\begin{array}{c}NH\\CH_2\end{array}\right\rangle CO} \longrightarrow \underset{\text{Indole}}{C_6H_4\left\langle\begin{array}{c}NH\\CH\end{array}\right\rangle CH}$$

It was first prepared by the reduction of indigo blue.

2. By leading ethylaniline or other alkyl derivatives of aniline—particularly cumidine—through a red-hot tube.

3. By the condensation of various *o*-substitution products of aniline (or of nitrobenzene, after preliminary reduction), *e.g.*, from *o*-amino-chloro-styrole on treatment with sodium ethoxide:

$$C_6H_4\left\langle\begin{array}{l}NH_2\\CH{=}CHCl\end{array}\right. + NaOC_2H_5 = C_6H_4\left\langle\begin{array}{c}NH\\CH\end{array}\right\rangle CH + NaCl + C_2H_5OH$$

4. From *o*-amino-benzyl cyanide by intramolecular rearrangement in presence of alkalis.[3] In this manner α-amino-indole is first produced, which then parts with ammonia to give indole.

The best preparative method consists in the reduction of indoxylic acid or of indoxyl in alkaline solution.[4]

Indole crystallises in plates, m.p. 52° and b.p. 245° (with partial decomposition). It is volatile in steam, and in the ordinary state possesses an unpleasant fæcal odour. After very careful purification, however, indole may be mixed in suitable dilution with other perfumes, with the surprising result that the odour of fresh flowers is imparted to the mixture. The presence of indole in jasmine-flower oil is therefore a very important factor in producing the specific perfume of jasmine.

Indole, like pyrrole, possesses weakly basic and at the same time somewhat phenolic properties. Similarly it is easily resinified with

[1] J. Herzfeld, *Biochem. Zeitsch.*, 1913, 56, 82.
[2] Weissgerber, *Ber.*, 1910, 43, 3520.
[3] R. Pschorr and Hoppe, *Ber.*, 1910, 43, 2543.
[4] Vorländer and Apelt, *Ber.*, 1904, 37, 1134.

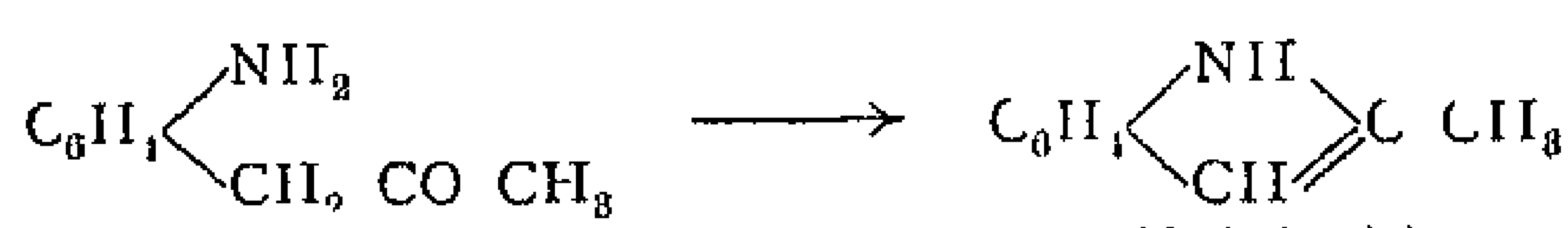
acids, and gives a cherry-red colour to a pine splint moistened with hydrochloric acid.

A large number of substitution products are known, the position of substituents being indicated by the use of α-, β-, N- or figures, as in the formula on p. 588.

ALKYL AND ARYL SUBSTITUTION PRODUCTS OF INDOLE

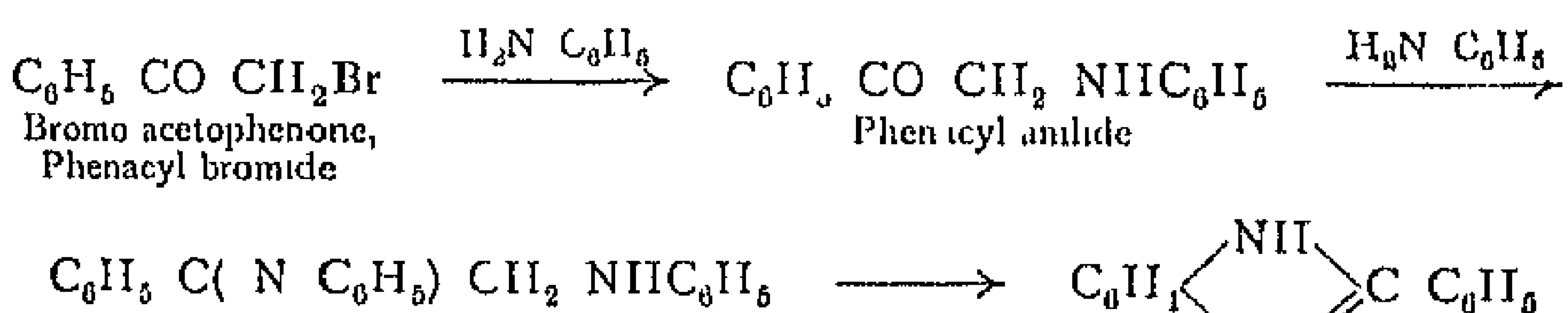
Homologues of indole occur in coal tar, and may be prepared from the higher fraction, b.p. 250° to 275°, of the technical crude indole.[1] They are synthesised by the following methods:—

1. In an analogous manner to the formation of indole itself by the condensation of aromatic *o*-amino-compounds, *e.g.*



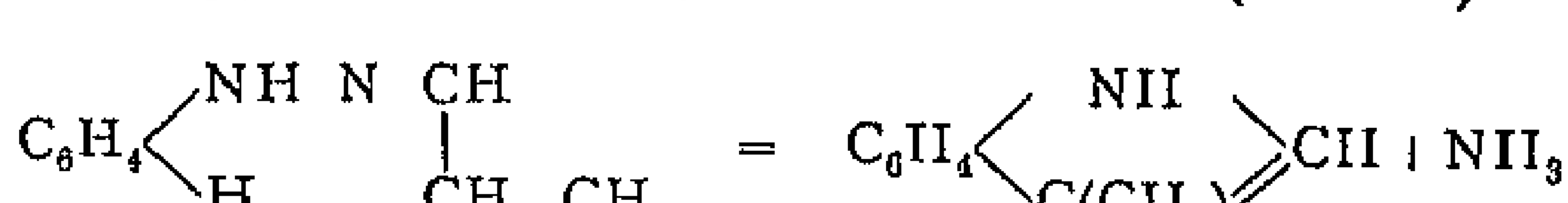
o-Aminobenzyl methyl ketone → α-Methyl indole

2. By the action of substituted anilines on anilides of ketones or aldehydes of the general formula, R′.CO.CH(NHC$_6$H$_5$).R″. Anilides of this type may be prepared from halogen derivatives of ketones and aldehydes, in which halogen is attached to the carbon atom adjacent to the carbonyl group, *i.e.*, from compounds containing the group —CO.CHCl—.[2]



Bromo acetophenone, Phenacyl bromide → Phenacyl anilide → α-Phenyl indole

3. By heating the phenylhydrazones of certain aldehydes and ketones, or of pyroracemic acid, with zinc chloride (Fischer).

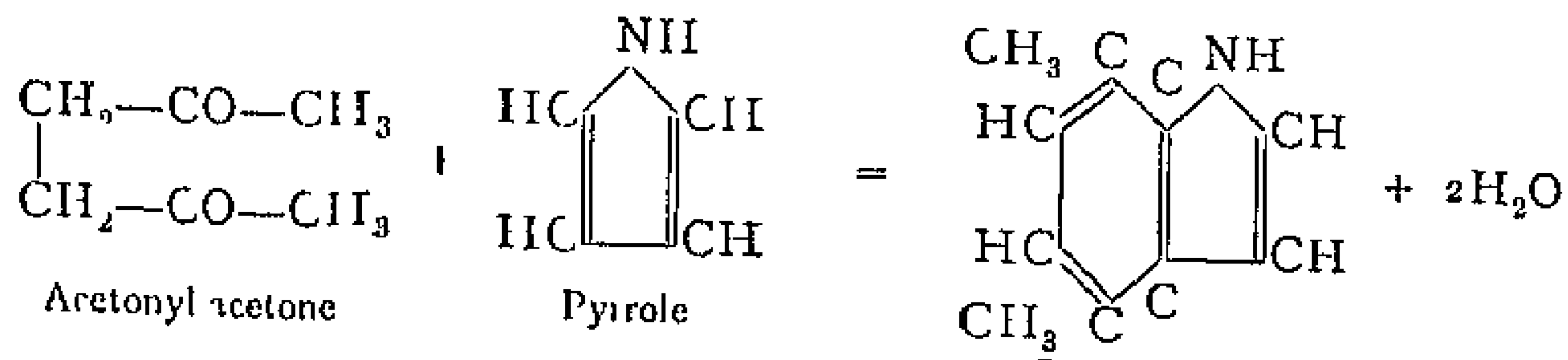


Propaldehyde phenylhydrazone = β-Methyl indole

The true homologues of indole, with the substituent in the pyrrole ring, are prepared chiefly by methods 1 and 3. But derivatives with the substituent in the benzene nucleus can also be obtained by these processes if use is made of starting materials substituted in the phenyl group. Thus 4.7-dimethyl-indole has been prepared from the *p*-xylyl-

[1] O. Kruber, *Ber.*, 1926, 59, 2752. [2] Hell and Cohen, *Ber.*, 1904, 37, 866.

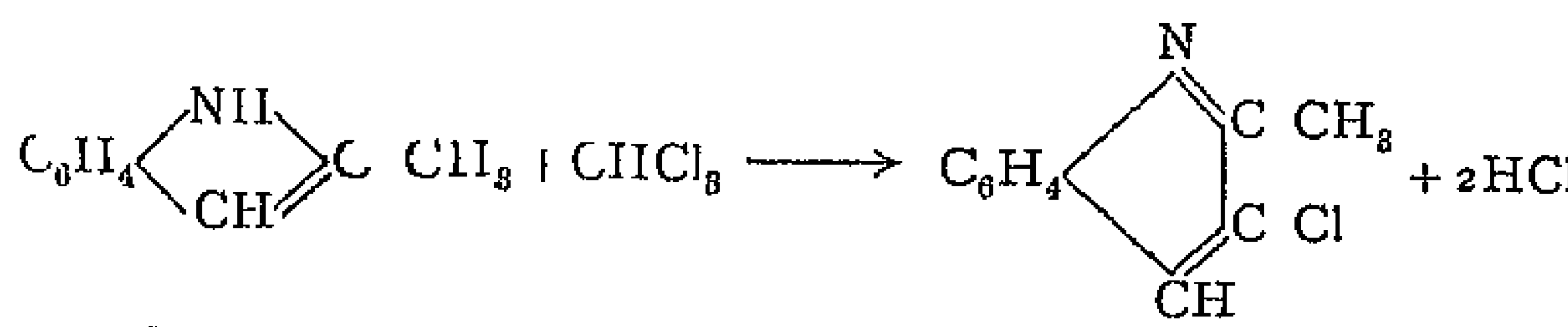
hydrazone of pyroracemic acid. Another interesting synthesis of this compound is from acetonyl acetone and pyrrole.[1]



Acetonyl acetone Pyrrole 4 : 7 Dimethyl indole

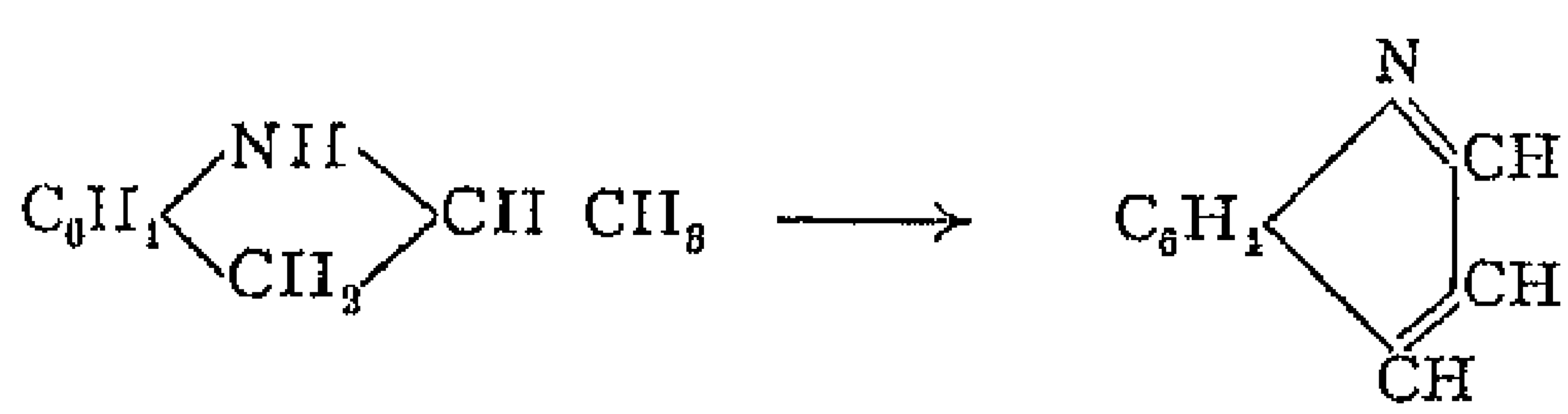
Alkyl-indoles resemble the parent compound in being of weakly basic character. The methyl derivatives have a repulsive smell, and on fusion with potash yield indole carboxylic acids. Most of them give the pine splint reaction.

Indole and its homologues (compare pyrrole, p. 568) react with chloroform or bromoform in such a way that the ring is extended and quinoline derivatives are produced. Chloroform and α-methyl-indole, for example, give β-chloro-quinaldine:



α-Methyl indole β-Chloro-quinaldine

The distillation of secondary hydro-methyl-indole derivatives over zinc dust also leads to the formation of the corresponding quinoline compounds:

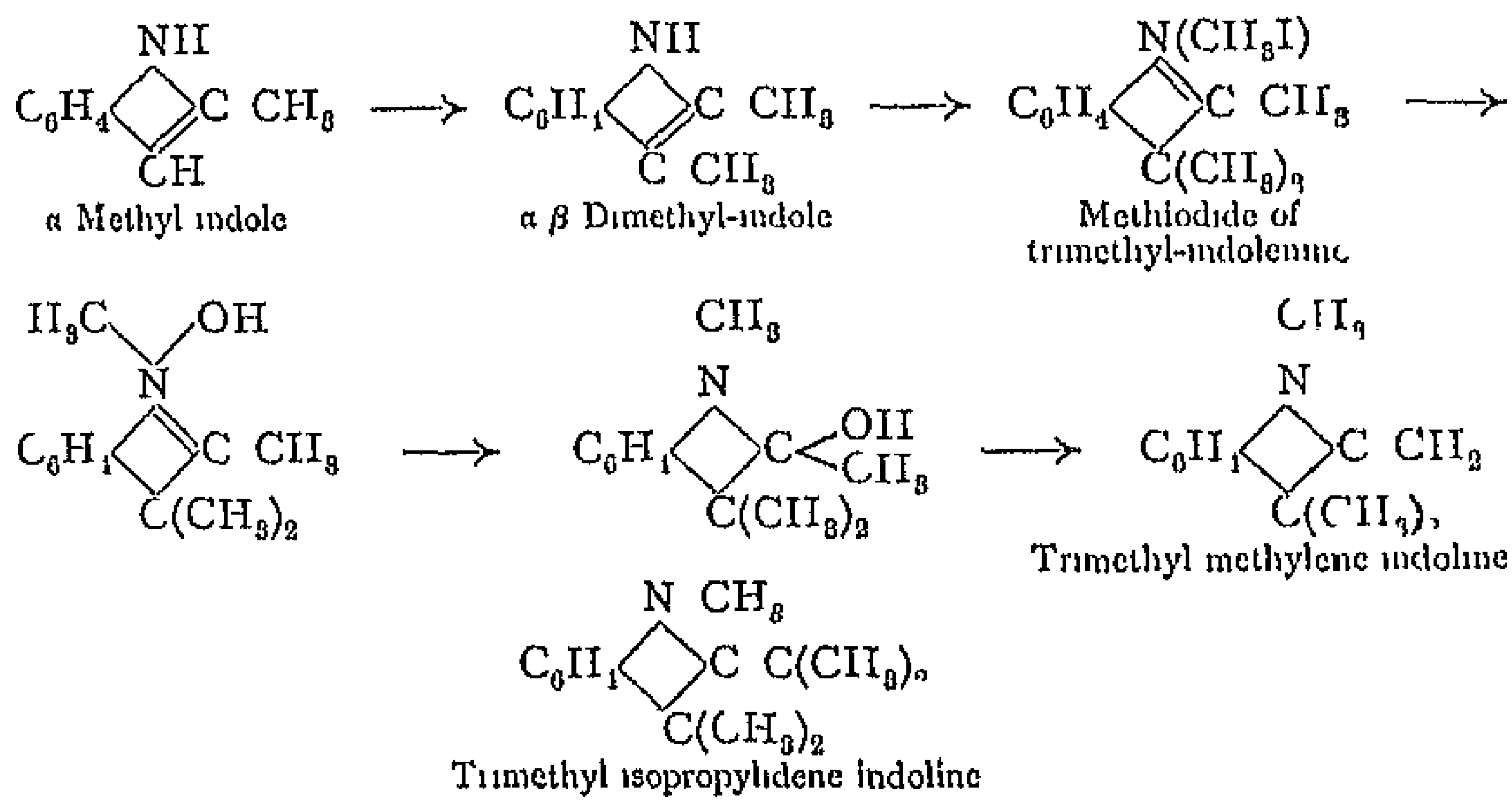


Hydro-α-methyl indole, α-Methyl-indoline Quinoline

The *behaviour of indole and alkyl-indoles on treatment with alkyl iodides* is of interest.[2] $\alpha\beta$-Dialkyl-indoles are first formed, without any alteration of the imino group: *e.g.*, α-methyl-indole yields $\alpha\beta$-dimethyl-indole. This, however, is only an intermediate phase. On further interaction with methyl iodide a rearrangement of the valency bonds takes place (transformation into the pseudo-form), the chief product being the methiodide of trimethyl-indolenine, together with a little hydriodide. On treatment with alkalis the first of these undergoes a remarkable change and is converted into trimethyl-methylene-indoline, which with methyl iodide takes up two more methyl groups

[1] *Ber.*, 1904, 37, 4236. [2] Ciamician, *Ber.*, 1904, 37, 4227.

to form trimethyl-isopropylidene-indoline. Even this, however, does not represent the end of the reaction, since the last-named compound may on the one hand yield a methiodide, and on the other its hydriodide under the influence of heat may exchange the isopropyl group for one of the methyl groups in the β-position. With the methylene group thus regenerated the above process may then repeat itself. The course of these reactions is indicated in the following scheme:



Skatole, *β-methyl-indole*, $C_8H_6(CH_3)NH$, is the best known homologue of indole. It is produced together with a little indole from albuminous matter by putrefaction or fusion with potash, and is also present in human fæces. As described on p. 590, it can be prepared from propylidene-phenylhydrazone. It crystallises in plates, m.p. 95°, b.p. 268°, and has a powerful and repugnant smell.

α-Methyl indole can be obtained from acetone-phenylhydrazone. It melts at 60°, boils at 268° and resembles indole in smell. *N-Methyl-indole* is an oil of boiling-point 240°, formed by eliminating carbon dioxide from the acid obtained from methyl-phenylhydrazine and pyroracemic acid. It has not the unpleasant smell of skatole.

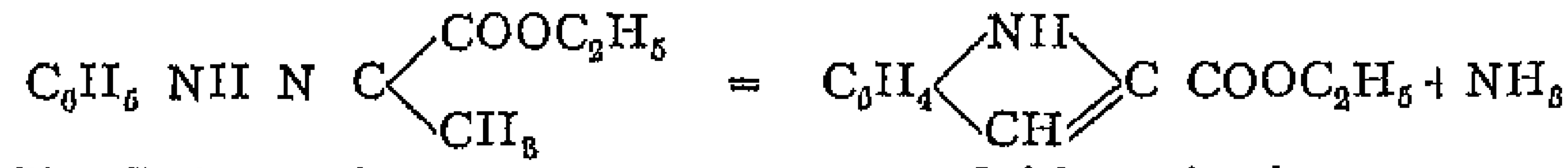
INDOLE CARBOXYLIC ACIDS

Most of the acids known in this series have been prepared by Fischer's method (previously described), which consists in heating the hydrazones of ketonic or aldehydic acids, such as pyroracemic acid and laevulinic acid, with zinc chloride.

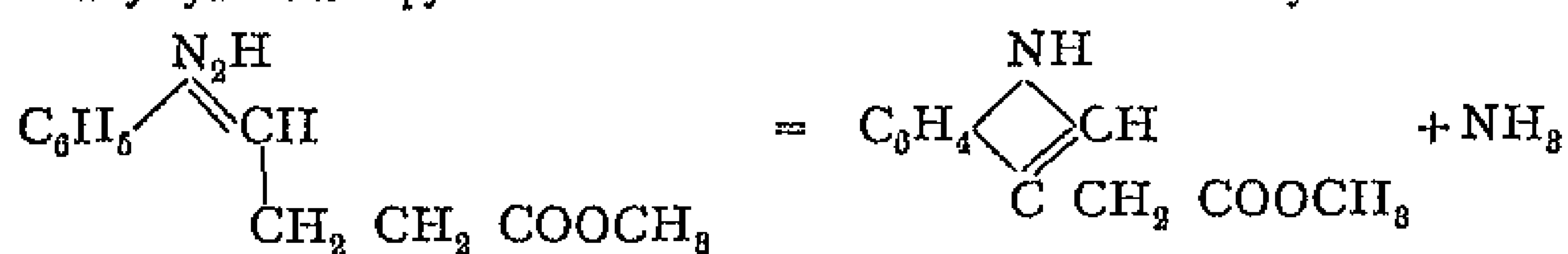
They may also be prepared in the manner already described by fusing alkyl-indoles with potassium hydroxide, or by the combined action of sodium and carbon dioxide on indoles.

The acids are solid, odourless compounds with distinctly acidic and

very little basic character They easily decompose into carbon dioxide and derivatives of indole



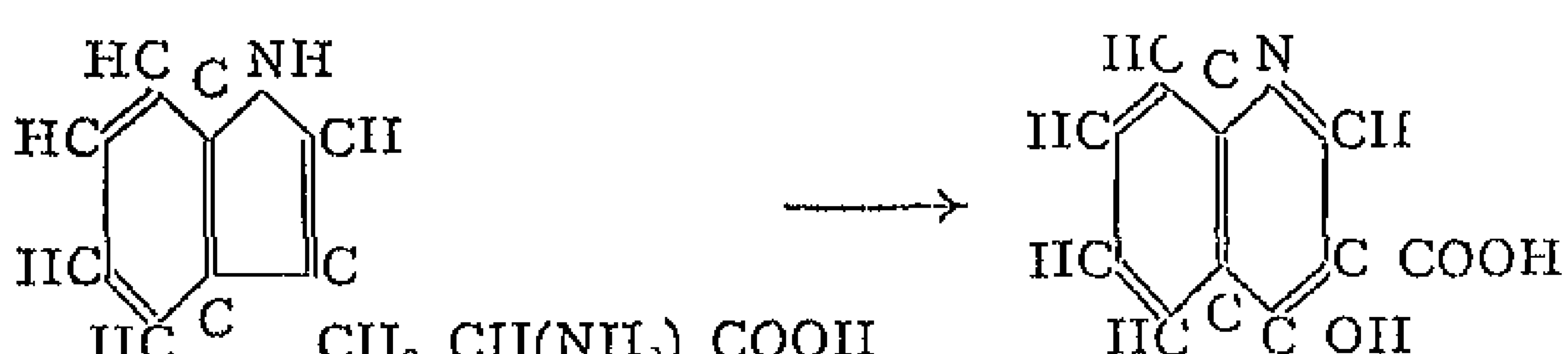
Phenylhydrazone of pyroracemic ester — Indole α carboxylic ester



Phenylhydrazone of β aldehydo-propionic ester — Ester of indole 3 acetic acid

Indole-3-acetic acid (formula see above) is formed during the decomposition of proteins, and has been synthesised by Ellinger according to the methods just quoted[1] It crystallises in small plates of melting-point 164°, and on heating above its melting-point decomposes into skatole and carbon dioxide For a long time this acid was assumed by a number of chemists to be 3-methyl-indole-2-carboxylic acid, and it will therefore be found frequently described as *skatole carboxylic acid*

Tryptophane is the compound which gives rise to all the derivatives of indole formed during the putrefaction of proteins It was first discovered by Hopkins and Cole[2] among the products of pancreatic digestion of casein In the organism of the dog it is converted into kynurenic acid Tryptophane has the following structure[3]



Tryptophane — Kynurenic acid, 4 hydroxy quinoline 3 carboxylic acid

Tryptophol, *3-indolyl-ethyl alcohol*, is formed in a similar manner to tyrosol (see p 448) when yeast is allowed to grow in a solution of tryptophane containing the usual addition of sugar and inorganic salts, or when tryptophane is fermented directly with much sugar and compressed yeast[1] It crystallises in needles or plates, and melts at 59°

Tryptophane — Tryptophol

[1] A Ellinger, *Ber*, 1904, 37, 1801, 1905, 38, 2884, 1906, 39, 2515 [2] Hopkins and Cole, *Journ of Physiol*, 1901, 27, 418 [3] Ellinger and Flamand, *Ber*, 1907, 40, 3029 R Majima, *Ber*, 1922, 55, 3859, 1924, 57, 1453 [1] F Ehrlich, *Ber*, 1912, 45, 883

HYDROXY DERIVATIVES OF INDOLE

Indoxyl, 3-hydroxy-indole, $C_6H_4{<}\begin{smallmatrix}NH\\ C\,OH\end{smallmatrix}{>}CH$, is present in the form of the potassium salt of indoxyl-sulphuric acid in the urine of mammals. It can be prepared by decomposing indoxylic acid with warm water.[1] Synthetic methods of formation will be described in connection with indigo. It forms bright yellow crystals, m.p. 85°; it cannot be satisfactorily distilled *in vacuo*, but may be partially volatilised without decomposition by heating in air or with slightly superheated steam. The vapours have a fæcal odour. When heated with potassium bisulphate indoxyl yields the salt of indoxyl-sulphuric acid, $C_8H_6N.O.SO_3K$, which on warming with acids easily reverts to indoxyl. In acid solution indoxyl has a strong tendency to resinify, and in the presence of alkalis is readily oxidised, even by atmospheric air, to give indigo.

According to the above formula, which is generally assumed for the solid compound, indoxyl contains the grouping $—C(OH)=CH—$. The presence of the hydroxyl group can be confirmed experimentally, but in many ways the compound reacts as the keto-form with the group $—CO—CH_2—$, thus giving rise to derivatives of the hypothetical *pseudo indoxyl*, $C_6H_4{<}\begin{smallmatrix}NH\\ CO\end{smallmatrix}{>}CH_2$.

Indoxylic acid, $C_6H_4{<}\begin{smallmatrix}NH\\ C.OH\end{smallmatrix}{>}C.COOH$, is of importance since it occurs as an intermediate product in the technical synthesis of indigo from phenylglycine-*o*-carboxylic acid. Its ethyl ester is obtained by reducing *o*-nitrophenyl-propiolic ester with ammonium sulphide:

$$\underset{o\text{-Nitrophenyl propiolic ester}}{C_6H_4{<}\begin{smallmatrix}NO_2\\ C\equiv C.COOC_2H_5\end{smallmatrix}} + 4H = \underset{\text{Ester of indoxylic acid}}{C_6H_4{<}\begin{smallmatrix}NH\\ C(OH)\end{smallmatrix}{>}C.COOC_2H_5} + H_2O$$

As mentioned above, it readily breaks up into carbon dioxide and indoxyl; with oxidising agents it yields indigo blue, and on heating with sulphuric acid is converted into the sulphonic acid of indigo blue.

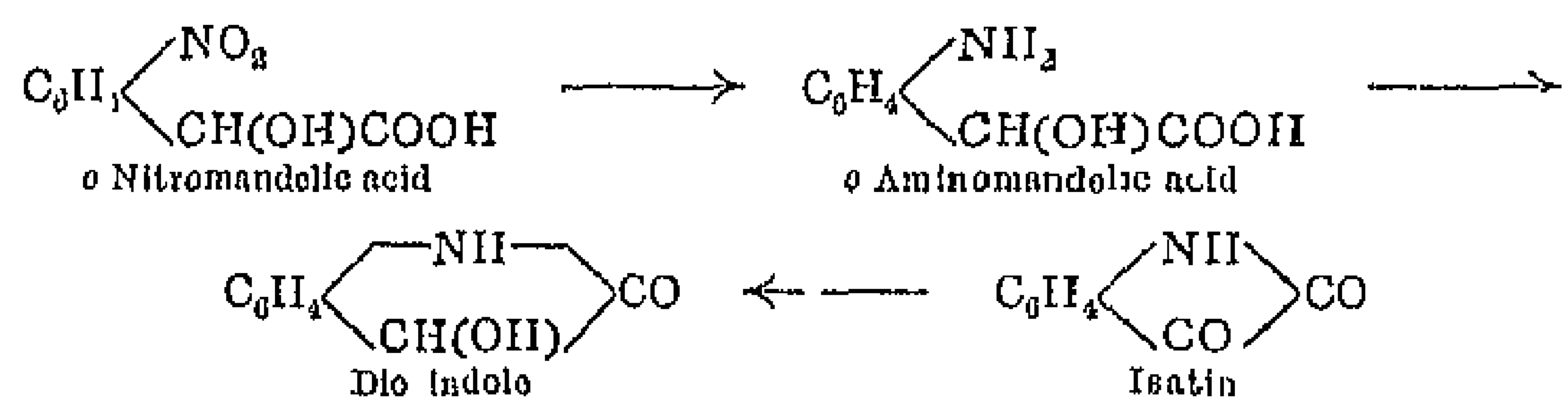
Oxindole is the lactam or inner anhydride of *o*-amino-phenylacetic acid. It is produced by reducing *o*-nitro-phenylacetic acid or dioxindole with tin and hydrochloric acid, or by reducing isatin with sodium amalgam.

$$\underset{o\text{-Nitrophenylacetic acid}}{C_6H_4{<}\begin{smallmatrix}NO_2\\ CH_2.COOH\end{smallmatrix}} \longrightarrow \underset{o\text{-Aminophenylacetic acid}}{C_6H_4{<}\begin{smallmatrix}NH_2\\ CH_2.COOH\end{smallmatrix}} \longrightarrow \underset{\text{Oxindole}}{C_6H_4{<}\begin{smallmatrix}NH\\ CH_2\end{smallmatrix}{>}CO}$$

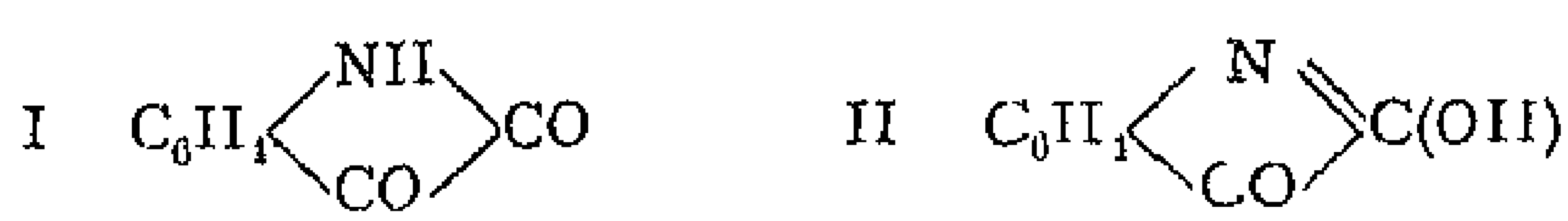
[1] Vorländer and Drescher, *Ber.*, 1902, **35**, 1701.

Oxindole crystallises in colourless needles, m p 120°, and possesses basic as well as acidic character, being soluble in both acids and alkalis The action of alkalis at higher temperatures ruptures the indole ring to form salts of *o*-amino phenylacetic acid Oxidising agents convert it first into dioxindole

Dioxindole is the lactam of *o* amino mandelic acid, and is formed in an analogous manner to oxindole by reduction of *o* nitromandelic acid with zinc dust and acetic acid, and also by reduction of isatin [1] It crystallises in colourless prisms, m p 180° On oxidation it yields isatin, and on reduction oxindole

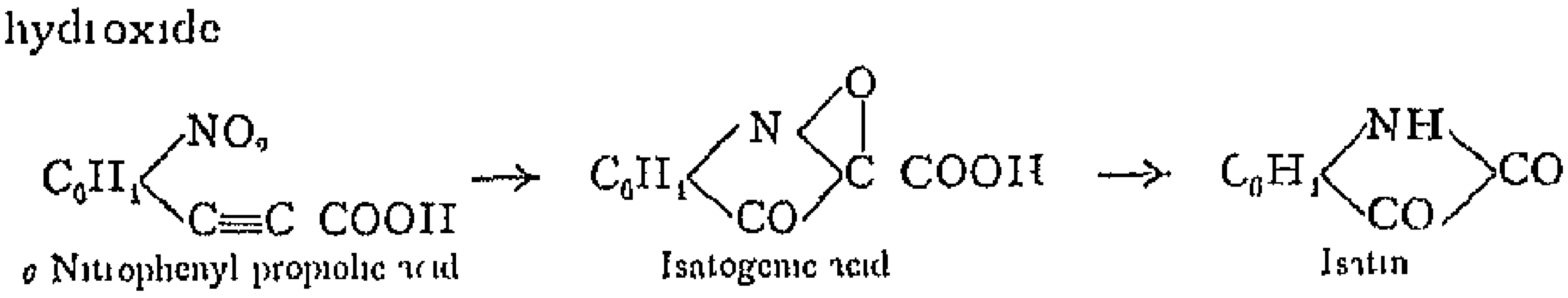


Isatin may react according to either of the formulæ I or II, and is therefore tautomeric



Structure I is ascribed to isatin in the solid state and in acid solution In salts [2] or alkaline solution, on the other hand, it possesses the structure II Isatin is therefore an inner anhydride which may react either as the *lactam* (I) or *lactim* (II) of *o*-amino benzoylformic acid, $NH_2 \cdot C_6H_4 \cdot CO \cdot COOH$ (isatic acid)

It is formed by oxidation of indigo blue with nitric or chromic acid, and also by oxidation of oxindole and dioxindole Among synthetic methods of preparation may be mentioned that involving the treatment of *o*-nitro-phenyl-propiolic acid with aqueous potassium hydroxide



Isatin crystallises in orange-red prisms, which melt at 200°, it dissolves sparingly in water, and readily in alcohol and ether When heated, it volatilises with partial decomposition It dissolves in alkalis, and if dilute solutions are employed the change from lactam to lactim structure (I to II) can be followed, the purple red colour of the N-salt passing at the ordinary temperature into the bright yellow of the O-salt If the solution is warmed, the ring opens with the production of the alkali salt of *o*-amino-benzoyl-formic acid or *isatic acid*, $NH_2 \cdot C_6H_4 \cdot CO \cdot COOH$

When fused with caustic alkali isatin yields aniline, and with

[1] Heller, *Ber*, 1904, 37, 939, 1907, 40, 1291 [2] Hantzsch, *Ber*, 1921, 54, 1257

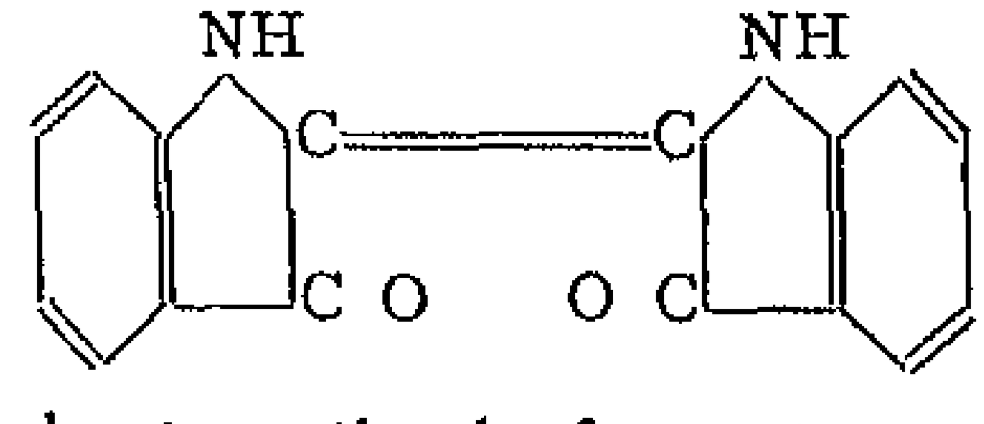
dilute nitric acid it is oxidised to nitro-salicylic acid From these reactions it was concluded that the compound contains a nitrogen and a carbon atom in direct union with the benzene nucleus Baeyer's investigation of the reduction products of isatin—dioxindole, oxindole and indole—finally led to the constitution of the compound being established, and therewith that of indigo The above formula for isatin, which had been proposed as early as 1869 by Kekulé, was also supported by the work of Claisen and Shadwell, who first showed that isatic acid was identical with *o*-amino-benzoyl-formic acid, and that isatin was its inner anhydride

The presence of a keto group in isatin is revealed by the usual reactions The compound unites with sodium bisulphite and gives a hydrazone with phenyl-hydrazine With hydroxylamine it yields *isatoxime*, $C_6H_4\left\langle\begin{matrix}-NH-\\C(NOH)\end{matrix}\right\rangle CO$, which is identical with the nitroso-oxindole obtained by the interaction of oxindole with nitrous acid

A number of isatin derivatives corresponding to the lactim structure (II) are also known For example, when the red silver salt of isatin is treated with methyl iodide the *methyl ether of isatin*, $C_6H_4\left\langle\begin{matrix}N\\CO\end{matrix}\right\rangle C\cdot OCH_3$, is formed, which crystallises from benzene in blood-red prisms of melting-point 101° to 102°. When warmed in benzene solution with phosphorus pentachloride, isatin yields *isatin chloride*, $C_6H_4\left\langle\begin{matrix}N\\CO\end{matrix}\right\rangle C\cdot Cl$, a brown crystalline compound which reverts to isatin on treatment with alkalis, and with ammonium sulphide gives indigo blue Halogens react with isatin to form substitution products, and nitric acid converts it into nitro-isatin, $C_6H_3(NO_2)\cdot C_2O_2NH$

Isatin gives a number of colour reactions It condenses with thiophene to give the blue dye-stuff *indophenine*, $C_{12}H_7NOS$ (see p 586), and with pyrrole to yield the blue *pyrrole-indophenine*, $C_{21}H_{18}N_4O_3$

Indigo Blue, Indigotin



Indigo blue or indigotin is the chief constituent of commercial indigo, the earliest and one of the most important of dye-stuffs It is mentioned by Dioscorides and Plinius, and in the thirteenth century Marco Polo described its preparation in India The dye was rapidly adopted in

Europe, and after the discovery of the sea route to India was imported in large quantities. Even to-day much of the natural indigo is obtained from India, although this is being displaced to an ever-increasing extent by the synthetic product. Indigo is of special importance for the dyeing of wool and is also used for cotton.

Occurrence and Production of Natural Indigo.—Indigo is prepared from a variety of plants, more particularly from those of the genus *indigofera* (India, China, Central America) and from woad (Hungary, France). In these sources it is not present as such, but in the form of **indican**, which is probably the glucoside of indoxyl,[1] $C_8H_6ON(C_6H_{11}O_5)$. Indican has a bitter taste, is laevorotatory and crystallises from water in prisms containing $3H_2O$. Under the influence of certain ferments, or when treated with dilute acids, it is hydrolysed into glucose and indoxyl, and the latter in contact with atmospheric oxygen becomes oxidised to indigo:

$$\underset{\text{Indican}}{C_{14}H_{17}NO_6} + H_2O = \underset{\text{Glucose}}{C_6H_{12}O_6} + \underset{\text{Indoxyl}}{C_8H_7NO}$$

$$\underset{\text{Indoxyl}}{2C_6H_4\left<\begin{matrix}NH\\C(OH)\end{matrix}\right>CH} + O_2 = \underset{\text{Indigo}}{C_6H_4\left<\begin{matrix}NH\\CO\end{matrix}\right>C=C\left<\begin{matrix}NH\\CO\end{matrix}\right>C_6H_4} + 2H_2O$$

The preparation of indigo in this manner is a comparatively simple process. Shortly before flowering the plants are cut down and brought into large stone cisterns or vats containing water at 25° to 30°. Enzymes present in the plant soon bring about hydrolysis of the indican, with the formation of glucose and indoxyl, the decomposition being complete in about ten to twelve hours. The liquid, which now contains ammonia in addition to indoxyl, is run off into vats at a lower level. Here it is "beaten," *i.e.*, brought into intimate contact with air by vigorous stirring with a stirrer or wheel. In this way the indoxyl is oxidised to indigo, which separates out in the form of blue flakes. The indigo is allowed to settle, and washed several times with water. It is finally boiled out with water, filtered and dried.

The natural indigo of commerce obtained in this way consists of blue lumps with a variable content of indigotin. Java indigo, for example, contains 60 to 80 per cent. of *indigo blue*, together with *indigo red* (indirubin), *indigo brown*, a glutinous substance known as indigo gelatin or indigo gluten, and ash. These substances may be removed by treating the indigo successively with water, dilute acetic acid, alkalis and alcohol.

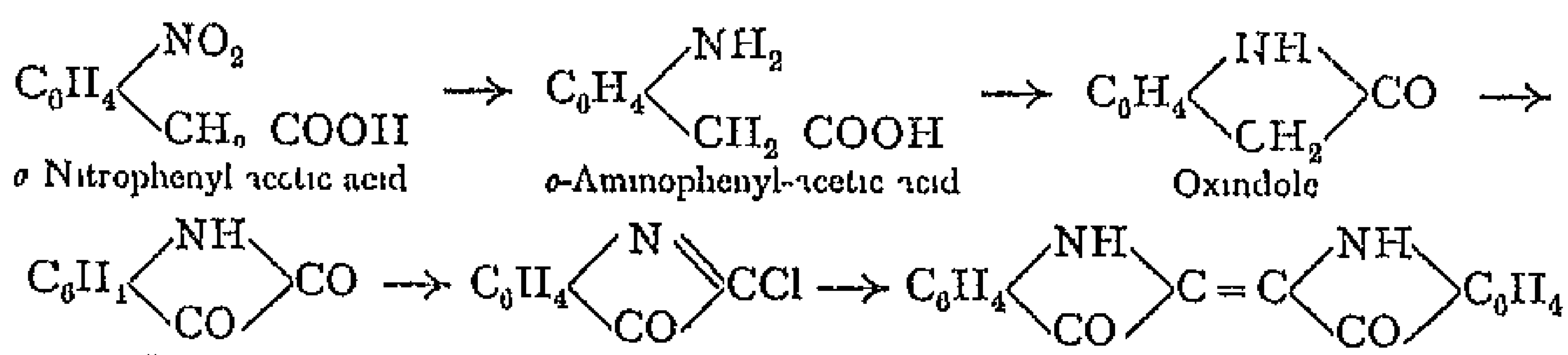
Synthesis of Indigo Blue

From the theoretical as well as the technical point of view the syntheses of indigo blue rank among the highest achievements of synthetic organic chemistry. One of these has already been mentioned

[1] See Macbeth and Pryde, *J. C. S.*, 1922, 121, 1660.

in connection with indoxylic acid and isatin. In the succeeding pages a short description is given of three syntheses possessing a purely scientific interest, followed in more detail by an account of the methods actually employed on the preparative scale.

1. The first and historic synthesis of indigo was carried out by Baeyer in the following stages:[1] *o*-Nitrophenyl-acetic acid was reduced to *o*-aminophenyl-acetic acid, which was readily converted into its lactam, oxindole. The latter, on treatment with nitrous acid, gave isonitroso-oxindole, and the amino oxindole obtained from this by reduction was transformed into isatin by the use of a mild oxidising agent. By treatment with phosphorus pentachloride isatin gave isatin chloride, which with zinc dust was reduced to indigo blue.

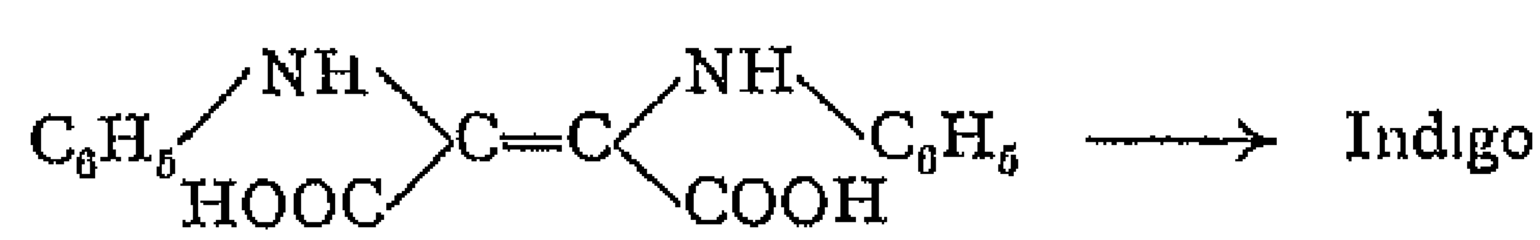


o-Nitrophenyl-acetic acid — *o*-Aminophenyl-acetic acid — Oxindole — Isatin — Isatin chloride — Indigo

2. Among other earlier syntheses of indigo, that from *o*-dinitro-diphenyl-diacetylene may be quoted, since it proves that in indigo the two indole nuclei are united to one another through a C-linking. The starting-point in this case was *o*-nitrophenyl-propiolic acid, which on boiling with water gave *o*-nitrophenyl-acetylene, $NO_2 \cdot C_6H_4 \cdot C : CH$. The copper compound of the latter, on oxidation with potassium ferricyanide, was converted into *o*-dinitro-diphenyl-diacetylene, and from this, on treatment with sulphuric acid and subsequent reduction, indigo was obtained.[2]

o-Dinitro-diphenyl diacetylene — Indigo

3. A later synthesis of Salmony and Simonis,[3] involving the elimination of water from dianilido-maleic acid, also shows the presence of a link between the *a*-carbon atoms of indigo blue.

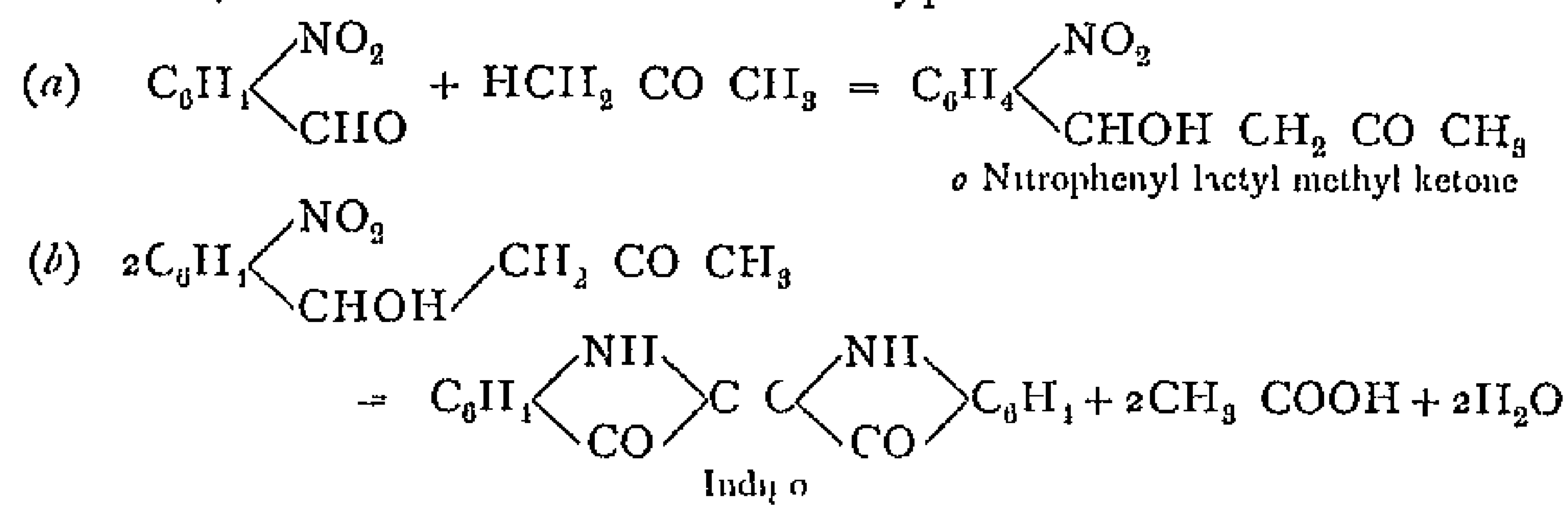


Dianilido-maleic acid

4. The synthesis discovered by Baeyer and Drewson[4] in 1882 is distinguished by its simplicity and ease of operation. It consists in

[1] Baeyer, *Ber.*, 1870, **3**, 514; 1878, **11**, 1228, 1296; 1879, **12**, 456. [2] Baeyer, *Ber.*, 1882, **15**, 50. [3] *Ber.*, 1905, **38**, 2580. [4] *Ber.*, 1882, **15**, 2856; **16**, 2205; *Ann.*, 1894, **284**, 154.

warming *o*-nitrobenzaldehyde with acetone and aqueous alkali, when *o*-nitrophenyl-lactyl methyl ketone is first produced as an intermediate product by a condensation of the aldol type

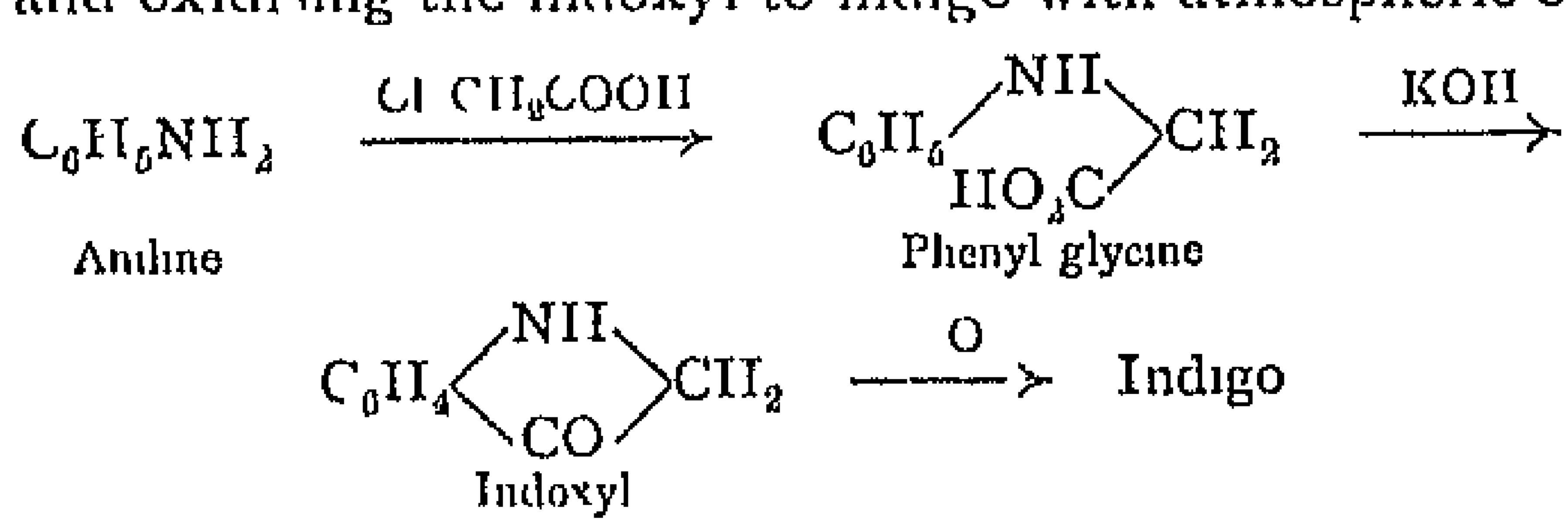


That part of the process formulated under (*a*) has been in use technically for a considerable time, the bisulphite compound of the above ketone being employed under the name of **indigo salt** for the generation of indigo in printing fabrics Nevertheless this method is not suitable for the manufacture of indigo on a large scale, owing to the difficulty of producing sufficient quantities of *o*-nitrobenzaldehyde

By employing substituted *o*-nitrobenzaldehydes this synthesis may be used to prepare substitution products of indigo Thus 2 4-dinitrobenzaldehyde,[1] on condensation with acetone in the presence of alkali, yields the corresponding **dinitro-indigo**, a dye of greenish-blue tint

Indigo can also be obtained from other compounds of similar type, *e g* from the aldehyde of *o*-nitrophenyl-β-hydroxy-propionic acid, $C_6H_4\langle^{CHOH\ CH_2\ CHO}_{NO_2}$, formed by condensing *o*-nitrobenzaldehyde with acetaldehyde

5*a* In 1890 a synthesis was proposed by Heumann[2] which for the first time gave promise of the successful manufacture of indigo on the technical scale, in so far as the requisite raw materials could be readily and cheaply obtained It consisted in allowing monochloracetic acid to interact with aniline to form phenylamino-acetic acid (phenyl-glycine, phenyl-glycocoll), converting this into indoxyl by fusion with potash, and oxidising the indoxyl to indigo with atmospheric oxygen



[1] Sachs, Kempf and Everding, *Ber*, 1902, 35, 1224, 1236, 1265, 2704 Friedländer and Cohn, *Monats*, 1902, 23, 543, 1003 [2] *Ber*, 1890, 23, 3043, 3431, 1893, 26, 225 *J pr Ch*, 1891, 43, 111, 1898, 57, 198

5*b* As this process only gave a small yield of indigo, Heumann modified it by using phenyl-glycine-*o*-carboxylic acid (prepared by condensing chloracetic acid with anthranilic acid) in place of phenylglycine in the potash fusion The indoxylic acid so obtained was converted into indigo by treating its alkaline solution with air

$$\underset{\text{Anthranilic acid}}{C_6H_4\left\langle\begin{matrix} NH_2 \\ COOH \end{matrix}\right.} \xrightarrow{Cl\,CH_2\,COOH} \underset{\text{Phenyl-glycine } o \text{ carboxylic acid}}{C_6H_4\left\langle\begin{matrix} NH\cdot CH_2\cdot COOH \\ COOH \end{matrix}\right.} \xrightarrow{KOH}$$

$$\underset{\text{Indoxylic acid}}{C_6H_4\left\langle\begin{matrix} NH \\ C(OH) \end{matrix}\right\rangle C\cdot COOH}$$

The discovery of a cheap method of preparing anthranilic acid from naphthalene, already described on pp 438 and 443, enabled the above synthesis to be operated commercially As now carried out, the process starts with the cheap raw material naphthalene and passes through the following stages

Naphthalene ⟶ *phthalic acid* ⟶ *anthranilic acid* ⟶ *phenyl-glycine-*o*-carboxylic acid* ⟶ *indoxylic acid* ⟶ *indoxyl* ⟶ *indigo*

As a result of this synthesis of indigo, **phenyl-glycine-*o* carboxylic acid** (m p 215° with decomp) and other aryl glycines have attracted a considerable amount of interest, and other methods have been developed for their industrial preparation

For example, anthranilic acid reacts with formaldehyde and hydrogen cyanide to form the nitrile of phenyl-glycine-*o*-carboxylic acid, which on hydrolysis yields the free acid, $C_6H_4\left\langle\begin{matrix} COOH \\ NH\cdot CH_2\cdot COOH \end{matrix}\right.$

The same reaction may be applied to aniline, which on treatment with formaldehyde and potassium cyanide gives the nitrile of phenylglycine, and on further hydrolysis **phenyl-glycine** itself

$$C_6H_5\cdot NH_2 + \underset{\text{Formaldehyde}}{H\cdot CH\,O} + KCN + H_2O = \underset{\text{Salt of phenyl glycine}}{C_6H_5NH\cdot CH_2\cdot COOK} + NH_3$$

According to Bucherer, the technical preparation of phenyl glycine is best effected by converting aniline and formaldehyde into anhydro-formaldehyde-aniline, $C_6H_5N:CH_2$, combining this with sodium bisulphite, and treating the resulting sulphonic derivative, $C_6H_5\cdot NH\cdot CH_2\cdot SO_3Na$, with potassium cyanide

In general, when sulphonates of the formula $R\cdot NH\cdot CHR'\cdot SO_3Na$ are treated in aqueous solution with potassium cyanide they yield

nitriles of aryl-glycines, as shown in the following equation (R = aryl group)[1]

$$\mathrm{R\cdot NH\cdot CH}{<}^{\mathrm{SO_3Na}}_{\mathrm{R'}} + \mathrm{KCN} \longrightarrow \mathrm{R\cdot NH\cdot CH}{<}^{\mathrm{R'}}_{\mathrm{CN}} + \mathrm{NaKSO_3}$$

The same compounds also result from the condensation of amine hydrochlorides with aldehydes, ketones, and their derivatives, in the presence of solid potassium cyanide suspended in benzene, ether or ligroin

$$\mathrm{R\cdot CHO + R'\cdot NH_2HCl + KCN = KCl + H_2O + R\cdot CH}{<}^{\mathrm{NH\cdot R'}}_{\mathrm{CN}}$$

Phenyl-glycine-*o*-carboxylic acid can also be obtained from *o*-chloro benzoic acid and glycine

$$\mathrm{C_6H_4}{<}^{\mathrm{COOH}}_{\mathrm{Cl}} + \mathrm{H_2N\cdot CH_2\cdot COOH} = \mathrm{C_6H_4}{<}^{\mathrm{COOH}}_{\mathrm{NH\cdot CH_2\cdot COOH}} + \mathrm{HCl}$$

This method is not expensive, as glycine can be prepared in good yield from chloracetic acid and ammonia

A detailed investigation of derivatives of phenyl-glycine-*o* carboxylic acid has revealed the fact that its esters and N-acylated and N-alkylated derivatives have a much greater tendency towards the formation of the indole ring than the unsubstituted acid[2] Thus the compound I is transformed into II merely on shaking with dilute alkali

$$\text{I}\quad \mathrm{C_6H_4}{<}^{\mathrm{N}{<}^{\mathrm{CH_3}}_{\mathrm{CH_2\cdot COOCH_3}}}_{\mathrm{COOCH_3}} \longrightarrow \text{II}\quad \mathrm{C_6H_4}{<}^{\mathrm{N(CH_3)}}_{\mathrm{CO}}{>}\mathrm{CH\cdot COOCH_3}$$

5*c* A discovery of practical importance is that, in the case of phenyl-glycine derivatives, ring formation can be effected with the aid of sodamide[3] as condensing agent Hence phenyl-glycine as well as its *o*-carboxylic compound is now used in the preparation of indigo on an industrial scale During the alkali fusion, as described on p 599, phenyl-glycine undergoes partial decomposition in consequence of the high temperature required (300° to 350°), and therefore gives a very low yield of indigo When sodamide is used, however, a much lower temperature suffices (180° to 240°), resulting in a greatly increased yield of the dye-stuff

$$\mathrm{C_6H_5\cdot NH\cdot CH_2\cdot COONa + NH_2\cdot Na} = \mathrm{C_6H_4}{<}^{\mathrm{CO}}_{\mathrm{NH}}{>}\mathrm{CH_2 + Na_2O + NH_3}$$

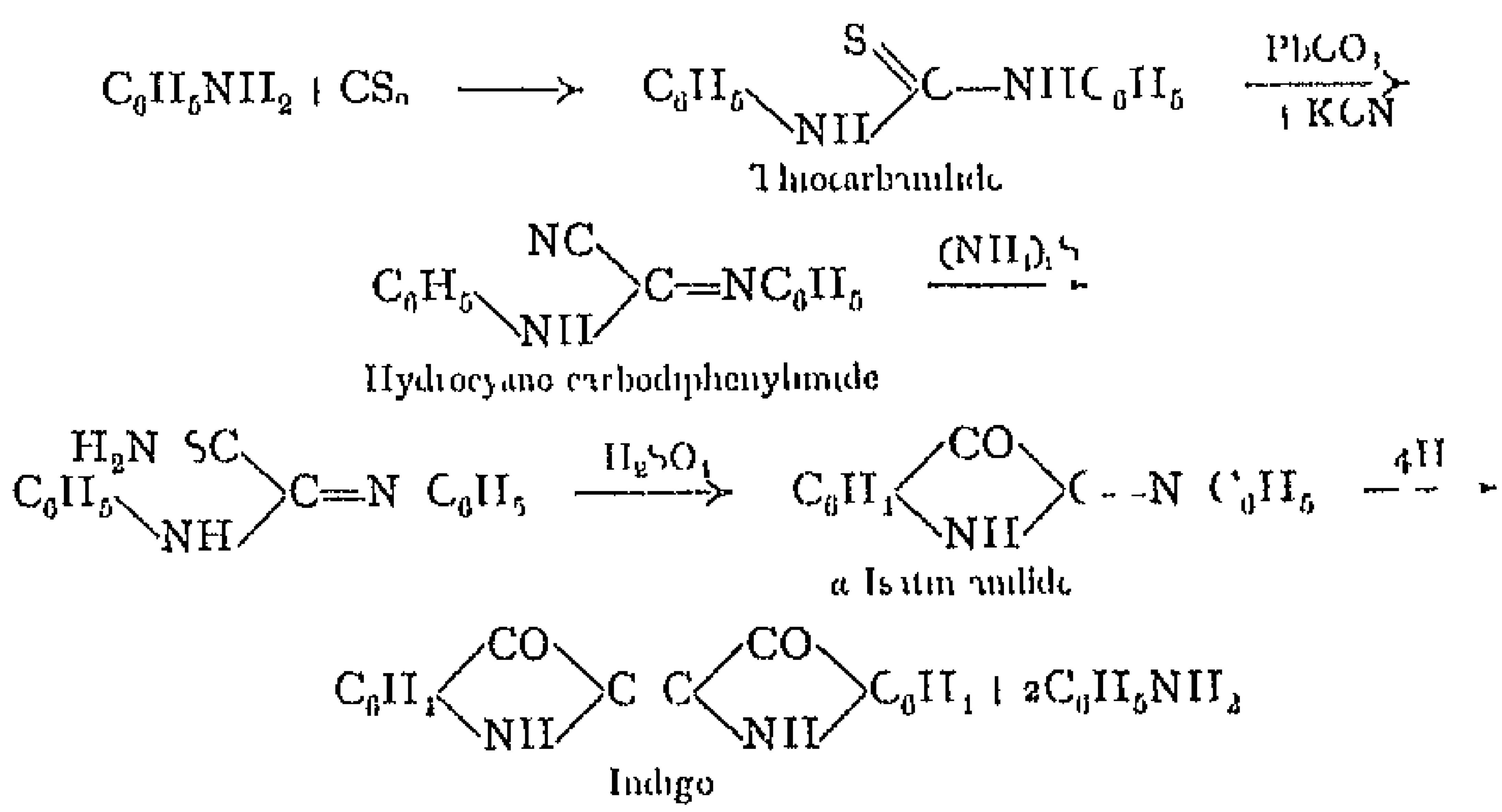
[1] Bucherer and Grolée, *Ber*, 1906, 39, 986 *Cf* also Zelinsky and Stadnikoff, *Ber*, 1906, 39, 1722 [2] Vorländer and co-workers, *Ber*, 1900 33, 553, 556, 3182, 34, 1646, 1649, 1854, 35, 700 [3] Sodamide is prepared by leading ammonia through liquid sodium

The *sodamide process*, which permits the use of phenyl glycine, or in the first instance of aniline, as the starting material, is operated on the large scale in the following stages

Benzene ⟶ *nitrobenzene* ⟶ *aniline* ⟶ *phenyl-glycine* ⟶ *indoxyl* ⟶ *indigo*

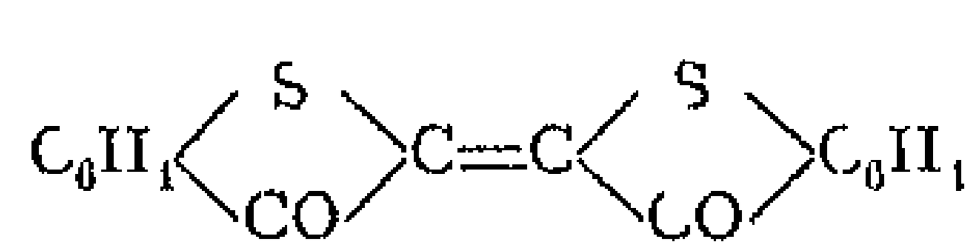
In recent years additional modifications, which cannot be described here, have been introduced into the Heumann synthesis

6 A method of synthesising indigo which has little in common with those described above was devised by Sandmeyer[1] Thiocarbanilide (diphenyl-thiourea, see p 384), obtained by the interaction of aniline and carbon bisulphide, is treated with basic carbonate of lead to remove sulphur, and then converted by means of potassium cyanide into hydrocyano carbodiphenylimide The latter with ammonium sulphide yields the corresponding thioamide, which on being warmed with concentrated sulphuric acid is condensed to α-isatin-anilide By heating this with ammonium sulphide it is readily transformed into indigo



For the synthesis of *sulphur analogues of the indigo group*, see P Friedlander, *Ber*, 1906, **39**, 1060 *Ann*, 1907, **351**, 390

The following compound prepared by Friedlander,

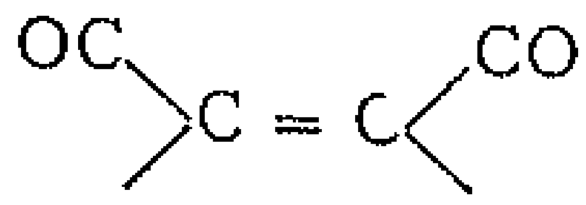


may be regarded as indigo blue in which the NH groups have been replaced by S It is used as a red dye, under the name of *thio-indigo red* With alkaline reducing agents it yields a reduction product

[1] *C*, 1900, II, 927, 929, 1141

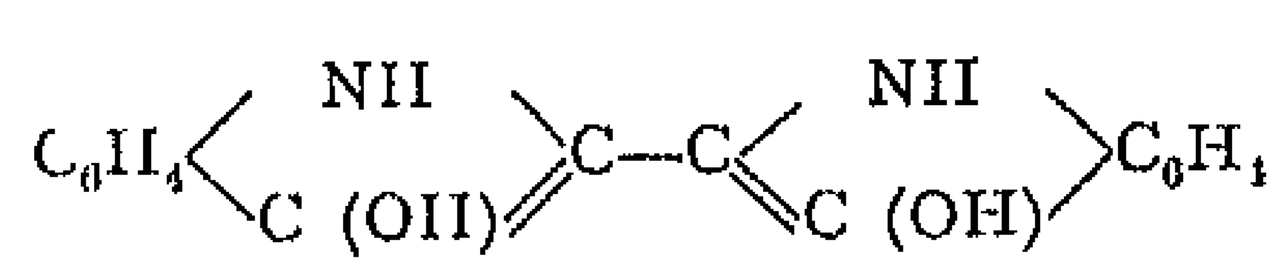
soluble in alkali, the solution of which, on oxidation in air, precipitates the original dye-stuff. In this manner it is deposited on the fabric. It gives a colour surpassing that of indigo in fastness to light and resistance towards oxidising agents.

Properties of Indigo Blue.—Indigo blue forms a dark blue powder possessing a reddish metallic lustre. In the light of our present knowledge of quinones and unsaturated diketones, it may be assumed that the colour of indigo is connected with the presence of the complex



in the molecule, in which the imido-groups play the part of auxochromes. The dye is insoluble in water, alcohol, ether, alkalis and dilute acids. It dissolves to a blue solution in hot aniline, and crystallises out from hot turpentine in blue plates. On sublimation it is obtained in coppery red prisms with a metallic glance. Cold concentrated sulphuric acid dissolves indigo without alteration, but on heating the green solution so obtained, the colour changes to blue, owing to the formation of sulphonic derivatives. Chlorine and bromine in the presence of water interact with indigo mainly to yield substituted oxidation products such as chloro-isatin. In the absence of water, on the other hand, substitution products of indigo are obtained which have attracted a good deal of attention of late. With bromine, for example, according to the proportion used, there is obtained **mono-** or **dibromo-indigo**. The brominated dyes are marked by their intensity of colour and beauty of tint, and in many cases may be used in place of indigo. These and other substitution products can also be prepared from corresponding substituted raw materials, by the methods already described for the synthesis of indigo.

With reducing agents indigo blue takes up two atoms of hydrogen and is converted into **indigo white**, which is formulated as a *di-indoxyl*



It possesses a phenolic character and dissolves readily in alkalis, to give a solution which in the presence of air undergoes rapid oxidation with precipitation of insoluble indigo blue. This property is of great importance and is utilised in the preparation of natural indigo from the plant (see p. 597), as well as in the process of vat dyeing.

Indigo is employed as a **vat dye**[1] in the following manner. Finely-divided indigo suspended in water is first reduced. According to the material to be dyed, this may be effected by use of fermentation

[1] For a description of the preparation and use of vat dyes, see Thorpe and Ingold, *Synthetic Colouring Matters, Vat Colours* (Longmans, Green, 1923).

methods or of various chemical reducing agents, such as ferrous sulphate, stannous chloride, grape sugar, zinc dust or hydrosulphite[1] The indigo white thus formed remains dissolved in the alkaline fluid

The material to be dyed is then steeped in the solution and exposed to air, when oxidation takes place and the indigo white is converted into indigo blue, which is deposited on the threads

In **cotton printing** with indigo, the dye suspended in concentrated caustic soda is pressed into contact with the fabric, which has previously been treated with a solution of glucose The material is then exposed to the action of steam, when indigo white is formed This penetrates into the threads, and on subsequent exposure to air is transformed into the blue dye The use of "indigo salt" has already been mentioned on p 599

In wool dyeing use is also made of the readily soluble sodium salt of indigo-disulphonic acid (see below), which is sent on to the market in the form of a paste under the name of **indigo carmine** This substance contains one sulphonic group in each benzene nucleus, in the para-position to the NH group, as has been shown by its synthesis by Heumann's method from anthranilido-acetic-*p*-sulphonic acid[2]

$$[1]\ HO_3S\ C_6H_3{<}\genfrac{}{}{0pt}{}{NH\ CH_2\ COOH[4]}{COOH} \longrightarrow$$

$$HO_3S\ C_6H_3{<}\genfrac{}{}{0pt}{}{NH}{CO}{>}C\ C{<}\genfrac{}{}{0pt}{}{NH}{CO}{>}C_6H_3\ SO_3H$$

Indirubin, indigo red, occurs together with its structural isomeride indigo blue in natural indigo It was synthesised by Baeyer by mixing weakly alkaline solutions of isatin and indoxyl, and may therefore be regarded as the indogenide of isatin

$$\underset{\text{Indoxyl}}{C_6H_4{<}\genfrac{}{}{0pt}{}{NH}{CO}{>}CH_2} + \underset{\text{Isatin}}{OC{<}\genfrac{}{}{0pt}{}{C_6H_4}{CO}{>}NH} = \underset{\text{Indirubin}}{C_6H_4{<}\genfrac{}{}{0pt}{}{NH}{CO}{>}C\ C{<}\genfrac{}{}{0pt}{}{C_6H_4}{CO}{>}NH} + H_2O$$

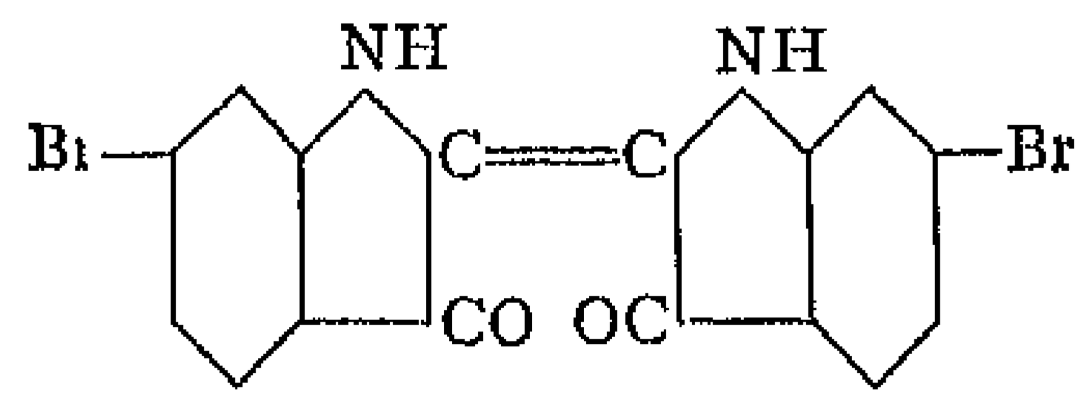
[1] The earliest vats employed were fermentation vats, still in common use to dye for woollen goods, in which the dye stuff is reduced by the action of micro organisms in the presence of lime or alkalis In the **woad vat**, for example, indigo suspended in water is treated with woad together with bran, madder, soda, and lime, and the mixture is stirred and heated to 50 Fermentation soon sets in and a yellowish solution of the calcium salt of indigo white is eventually formed It is necessary to exclude air, as the micro organisms are then forced to satisfy their need for oxygen by reducing the indigo blue Compare Wendelstadt and Binz, *Ber*, 1906, 39, 1627

The best vat for cotton is the **hydrosulphite vat**, in which the reducing agent is the soluble sodium salt of hydrosulphurous acid, $H_2S_2O_4$ It is prepared by mixing zinc dust with a solution of sodium bisulphite and, when reduction is complete, adding milk of lime, the liquid is then drawn off from the resulting precipitate ($CaSO_4$ and zinc salts) A solution of sodium hydrate is added, together with a paste of indigo and water, and the mixture warmed with stirring to 60°, when a concentrated alkaline solution of indigo white is formed From this "stock vat" the dyeing vats are obtained by dilution with water

[2] Vorländer and Schubart, *Ber*, 1901, 34, 1860

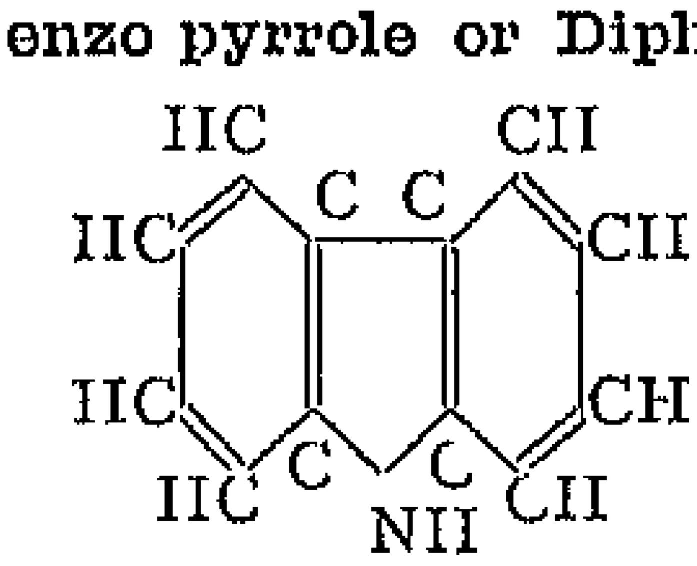
Baeyer describes as **indogenides** those compounds in which an oxygen atom is replaced by the indogen group, $C_6H_4\left\langle\begin{matrix}NH\\CO\end{matrix}\right\rangle C=$

6 6′-Dibromo-indigo, of the formula



is a substance of particular interest, being identical with the *purple of the ancients* (Tyrian purple) This has been proved by a direct comparison of the synthetic product with that prepared from the secretion of the Purple Snail, *Murex brandaris*[1] The same dye can also be obtained from other molluscs,[2] such as *Murex trunculus*, *Purpura lapillus*, and *Purpura aperta* It forms crystals of a coppery glance, and by interaction with caustic soda and sodium hydrosulphite yields a vat of weak yellow tint from which cotton is dyed a reddish-violet shade This striking displacement of the colour of indigo results not only from the introduction of bromine, but also of chlorine and methoxyl groups in the 6 6′-positions Hence substitution in the *p*-position to the CO-group exerts a quite specific influence In the same way the effect of *p*-substitution may be traced in the derivatives of thio-indigo **Tetrabromo-indigo,** which in colour and fastness possesses advantages over the parent dye, can be prepared by direct bromination of indigo, or by synthesis from 3 5-dibromo-anthranilic acid[3]

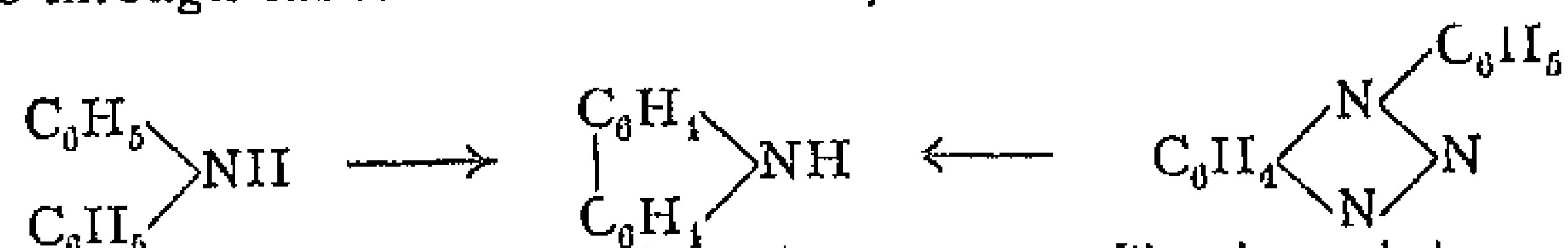
Carbazole, Dibenzo pyrrole or Diphenylene imine[4]



As has been mentioned on p 534, carbazole is found in crude anthracene The hydrogen atom of the imino-group resembles that of pyrrole in being replaceable by metals, and hence carbazole may be isolated from the above source in the form of potassium carbazole, $C_{12}H_8NK$, by distilling crude anthracene over potassium hydroxide Another method involves treatment with suitable solvents It is

[1] P Friedlander, *Ber*, 1909, 42 765 *Ann*, 1912, 388, 23 [2] Friedlander, *Ber*, 1922, 55, 1655 [3] Ullmann and Kopetschni, *Ber*, 1911, 44, 425 [4] See monograph by G Cohn, *Die Carbazolgruppe* (Leipzig, 1919)

produced synthetically by various reactions, *e.g.* by leading diphenylamine through tubes heated to redness,



Diphenylamine Carbazole Phenyl azimido benzene

and from thio-diphenylamine by the removal of sulphur with copper powder. It can also be obtained from *o*-amino-diphenylamine. With nitrous acid the latter yields phenyl-azimido-benzene, which on distillation parts with nitrogen to form carbazole. The last method is capable of general application, and by its means substitution products of carbazole may be prepared. Carbazole is also obtained by heating *o*-diamino-diphenyl to 200° with 25 per cent. sulphuric acid, when ammonia is eliminated between the two amino-groups.

At the ordinary temperature carbazole is only sparingly soluble in the majority of solvents; it crystallises in leaflets or plates which melt at 238° and boil at 354° to 355°. Like pyrrole it is a very weak base and only forms a stable salt with picric acid. It also resembles pyrrole in giving a deep red colour with a pine splint. With isatin and sulphuric acid, a blue coloration is produced.

Carbazole is an extremely stable compound. It may be distilled unchanged over zinc dust at a red heat, and is not attacked by concentrated hydrochloric acid or alcoholic potash, even at 300°.[1] Towards potassium permanganate it behaves as a fully saturated substance.

The derivatives of carbazole, which cannot be discussed here, are as yet comparatively incompletely investigated, probably owing to the difficulties encountered in working with this substance.

III

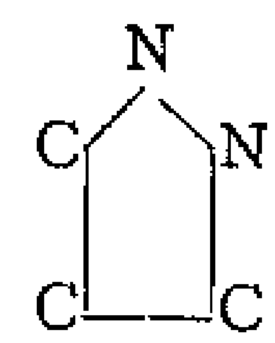
Azoles

Under the name of "azoles" are included various five-membered cyclic systems containing nitrogen. In addition to carbon and nitrogen these rings may also contain oxygen or sulphur. Hence they may be derived from the compounds pyrrole, furfurane and thiophene, described in the previous chapter, by replacing methine groups with nitrogen atoms. Only the most important of these will be described in detail.

[1] For hydro derivatives of carbazole, see J. Schmidt and co-workers, *Ber.*, 1907, **40**, 3225; 1912, **45**, 1779. Borsche, *Ann.*, 1908, **359**, 49. W. H. Perkin, jun., and P. Plant, *J. C. S.*, 1924, **125**, 1503.

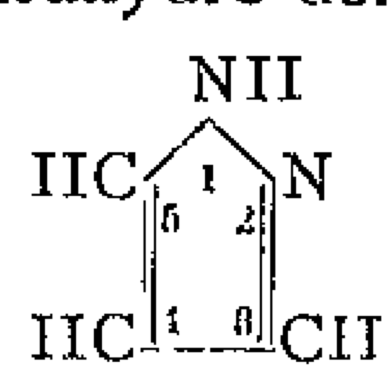
I.—PYRAZOLE GROUP

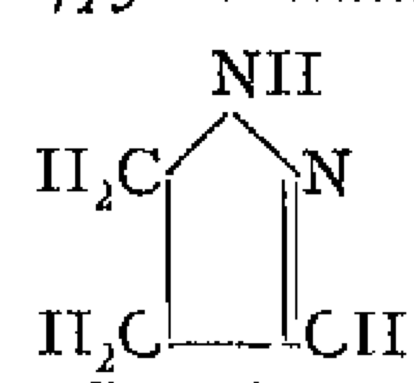
This group comprises all those compounds, the molecules of which contain a ring composed of three carbon and two nitrogen atoms arranged as follows:[1]

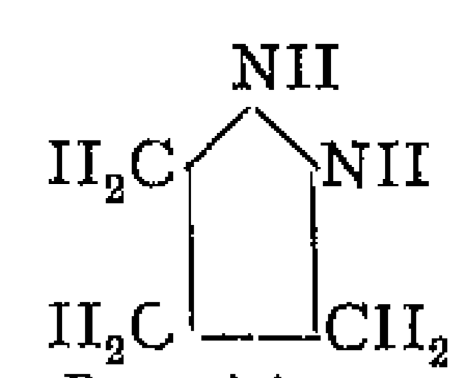


The parent substance of these compounds, pyrazole, is a pyrrole in which a methine group has been replaced by nitrogen.

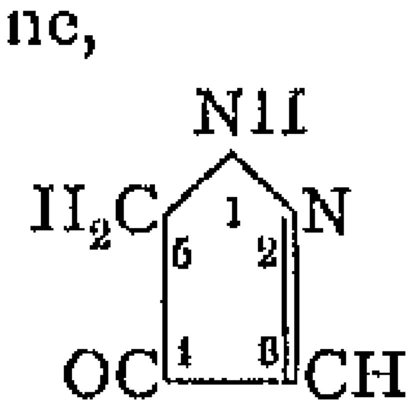
For this reason *the nomenclature of the pyrazole group* is based on that suggested by Knorr for pyrrole derivatives. Just as dihydro-pyrrole is known as pyrroline and tetrahydro-pyrrole as pyrrolidine, so the dihydro-pyrazoles are termed *pyrazolines* and the completely reduced tetrahydro-derivatives, *pyrazolidines*.

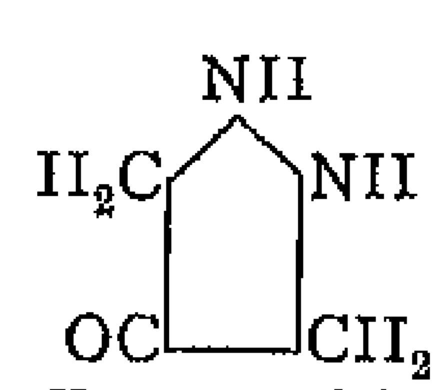

Pyrazole


Pyrazoline

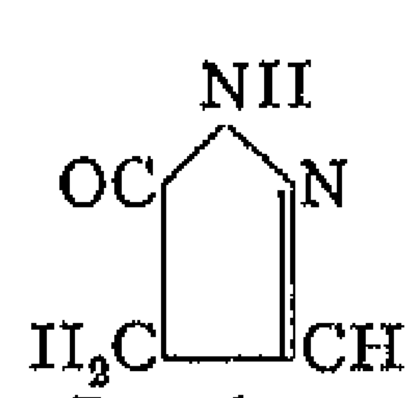

Pyrazolidine

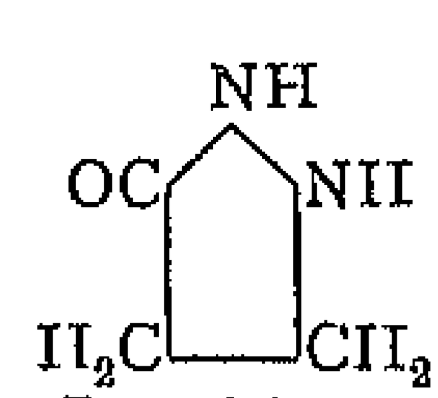
The position of a substituent group in the pyrazole nucleus is indicated by the numbers 1 to 5. Numbering commences with the nitrogen atom of the imino-group and proceeds in a clockwise direction to the second nitrogen atom, as in the above formula. Ketonic derivatives of pyrazoline and pyrazolidine are usually divided into two classes, viz., 4-derivatives or true ketones, such as keto-pyrazoline and keto-pyrazolidine,


Keto-pyrazoline


Keto pyrazolidine

and the 3- and 5-derivatives, which are cyclic acid amides. For the latter, Knorr proposed the names pyrazolone and pyrazolidone.


Pyrazolone


Pyrazolidone

[1] Literature: L. Knorr, *Ann.*, 1894, 279, 188; 1896, 298, 1; 1903, 328, 62. J. Schmidt, "Ueber die Pyrazolgruppe" (*Ahrens Vorträge*, vol. iv., Stuttgart, 1899).

Our knowledge of the pyrazole series is largely due to the work of Knorr, who described the first representatives of this group in 1883[1] The physical properties of these compounds and the applications which many of them, such as antipyrin, find in medicine, lend a special interest to this chapter of organic chemistry For this reason the pyrazole group, after its discovery by Knorr, was investigated in a number of directions and—thanks to the ease with which the pyrazole ring can be formed—these efforts met with considerable success Among other results, it may be mentioned that Knorr has established the existence of a peculiar type of isomerism in this series, which appears to throw some light on the structure of benzene

General Methods of Preparing Pyrazole Derivatives

Various means of synthesising pyrazole derivatives have been developed by Knorr

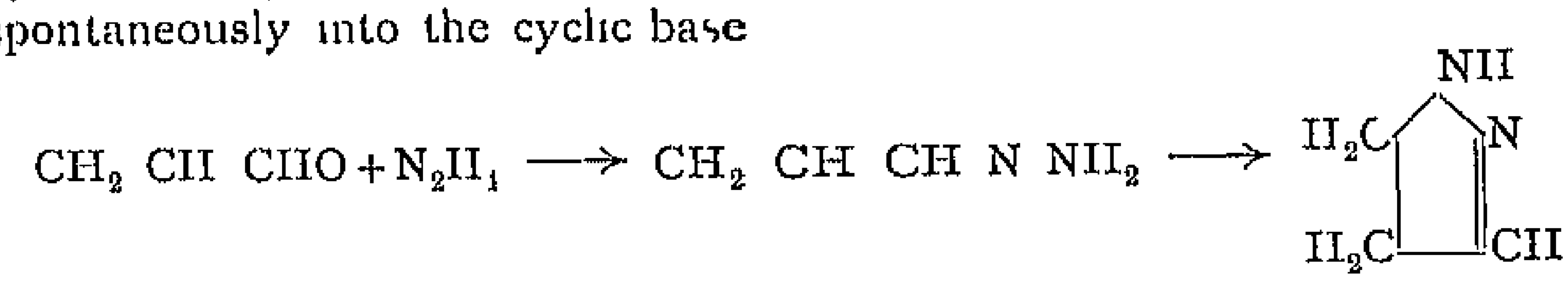
Esters of β-ketonic acids condense with hydrazines to form derivatives of pyrazolone The reaction proceeds in two phases A hydrazone of the ester is first produced, from which alcohol is then eliminated (See p 261)

A method similar to the above consists in the interaction of hydrazines with β-diketo-compounds of the general formula R′ CO CHR″ COR‴ (see p 251) This has proved the most fruitful of all reactions devised for the preparation of pyrazole derivatives On the one hand, as basic component, we may employ hydrazine hydrate itself or any primary hydrazine, and on the other, the above general formula includes all the numerous β-diketones and β-keto-aldehydes which can be prepared by the synthetic methods of Claisen and Wislicenus

Hydrazines condense with unsaturated ketones or aldehydes of the types

$$R'—CO—CR'=CHR'' \quad \text{and} \quad H—CO—CR'=CHR''$$

to give derivatives of pyrazole or pyrazoline Thus the parent compound of the latter class, **pyrazoline**, is formed from acrolein and hydrazine hydrate The acryl-hydrazine first obtained isomerises spontaneously into the cyclic base



Phenyl-hydrazones of unsaturated aldehydes and ketones, containing a double bond in the α position, may be transformed with great ease into the isomeric pyrazoline derivatives by boiling with glacial acetic acid[2]

[1] L Knorr, *Ber*, 1884, 17, Ref 149 [2] K Auwers and co workers, *Ber*, 1908, 41, 4230, 1909, 42, 4411

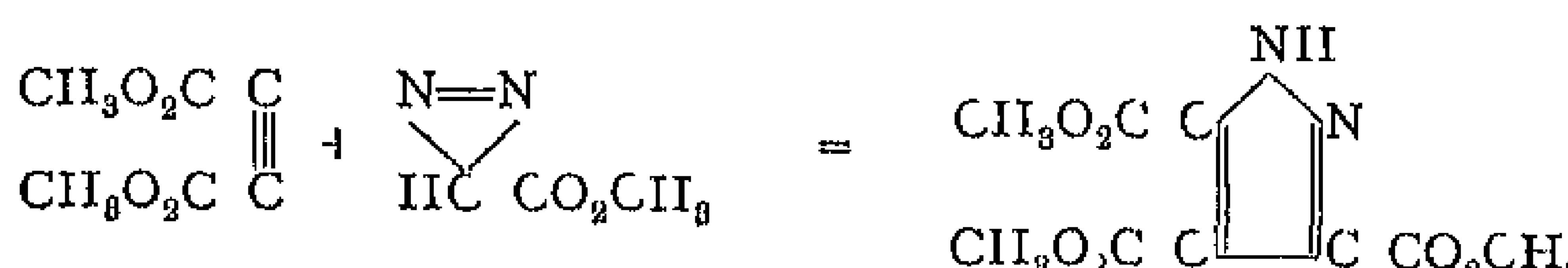
In a similar manner unsaturated acids of the acrylic acid series, R.CH CH COOH, react with hydrazines to give derivatives of pyrazolone or pyrazolidone[1]

The principle of the above syntheses may be summarised in the following statement

Compounds containing two CO-groups, or a CO- and a COOH-group, in the β-position to one another, or two doubly linked carbon atoms adjacent to a COOH- or CO-group, react with hydrazines to give pyrazole derivatives

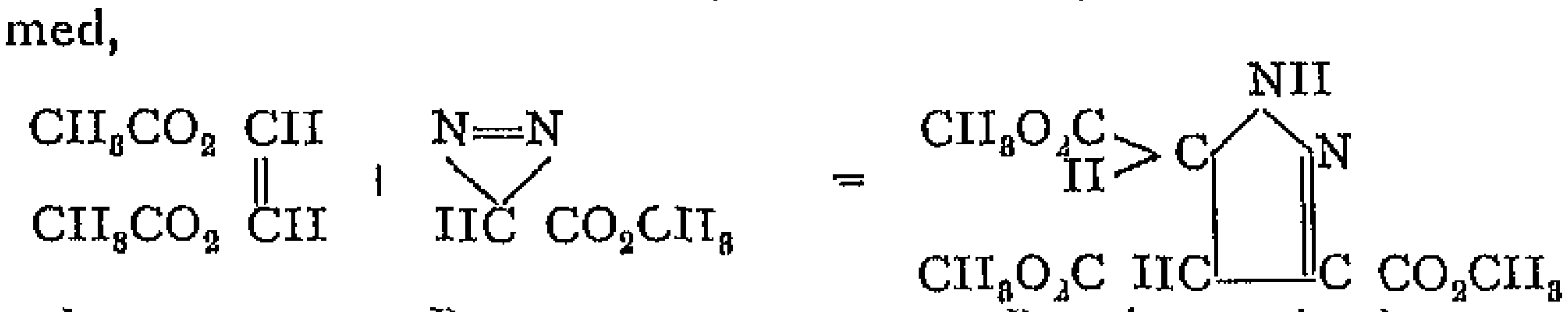
Further syntheses in this group have been effected by E Buchner in the course of an investigation into the action of diazo-acetic ester on unsaturated compounds[2] Pyrazole derivatives were obtained

(*a*) By the interaction of diazo-acetic ester with esters of mono or dibasic acids of the acetylene series,



Acetylene dicarboxylic ester — Diazo acetic ester — Pyrazole tricarboxylic ester

(*b*) By combination of diazo-acetic ester with ethylene derivatives such as esters of fumaric acid, in this case pyrazoline derivatives are formed,



Fumaric ester — Diazo-acetic ester — Pyrazoline-tricarboxylic ester

(*c*) By the action of diazo acetic ester on esters of certain saturated or unsaturated halogen substituted acids (*e g*, bromo maleic acid, α bromo cinnamic acid, α β dibromo propionic acid),

$$\underset{\text{Dibromo propionic ester}}{C_2H_3Br_2(CO_2CH_3)} + \underset{\text{Diazo acetic ester}}{3CHN_2(CO_2CH_3)} = \underset{\text{Pyrazole dicarboxylic ester}}{C_3H_2N_2(CO_2CH_3)_2} + \underset{\text{Bromo acetic ester}}{2CH_2Br(CO_2CH_3)} + 2N_2$$

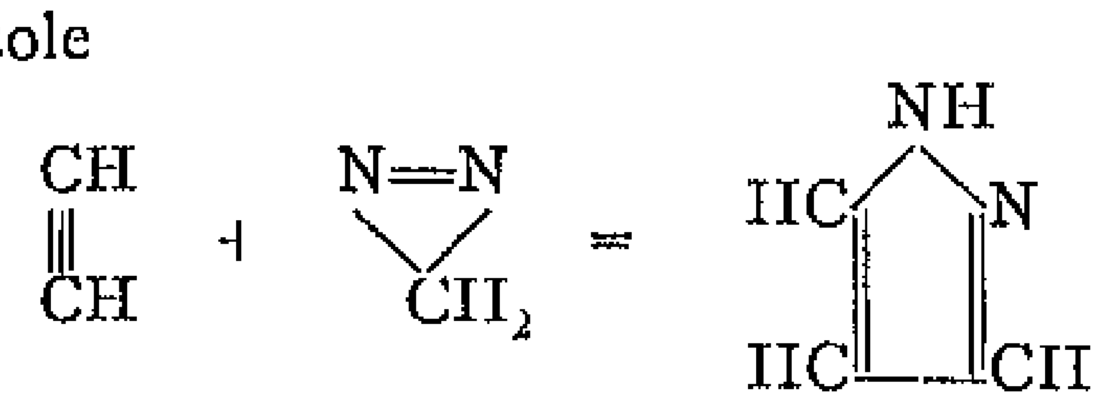
The **preparation of pyrazole** itself was first accomplished by the above methods E Buchner obtained it in 1889 by the prolonged action of heat on 3 4 5-pyrazole tricarboxylic acid, the ester of which is formed, as just described, by the addition of diazo-acetic ester to acetylene-dicarboxylic ester

Soon afterwards it was prepared by Balbiano by heating hydrazine hydrate with epichlorhydrin and chloride of zinc

Subsequently von Pechmann discovered that acetylene and diazo-

[1] Knorr and Duden, *Ber*, 1892, 25, 761   [2] *Ann*, 1893, 273, 214

methane react in a similar manner This constitutes the simplest synthesis of pyrazole



Pyrazole is also obtained by treating the acetal of propargyl-aldehyde[1] with hydrazine

$$\underset{\text{Propargyl acetal}}{CH \equiv C \cdot CH(OC_2H_5)_2} \xrightarrow{+H_2N \cdot NH_2} \underset{\text{hypothetical intermediate product}}{CH \equiv C \cdot CH : N \cdot NH_2} \longrightarrow \underset{\text{Pyrazole}}{CH : CH \cdot CH : N \cdot NH}$$

These simple syntheses prove that the atoms in the pyrazole ring are arranged in agreement with the formula assumed above

Probably the best means of preparing pyrazole is from pyrazole-3 5-dicarboxylic acid This is readily prepared synthetically, and on being heated decomposes smoothly into carbon dioxide and pyrazole (Knorr)

In connection with this survey of the synthetic methods available for preparing pyrazole derivatives, some reactions of the latter may be quoted which are of value in the preparation of simpler members of the series

A reaction of special importance for the preparation of pyrazole itself consists in the elimination of carboxyl groups from pyrazole-carboxylic acids, by heating the latter above their melting-points

The conversion of the oxygen derivatives, pyrazolones and pyrazolidones, into pyrazoles may be effected by distillation with zinc dust, or more conveniently by the action of phosphorus pentasulphide or tribromide[2]

The oxygen of pyrazolones may also be removed by heating these substances with phosphorus oxychloride, when chloro-derivatives are formed (Michaelis)

Properties of Pyrazole and its Derivatives

The similarity in the formulæ of pyrazole and pyrrole does not extend to their properties Pyrazole differs strongly from pyrrole in its remarkable stability and more definitely basic character

Pyrrole turns brown in air, resinifies with extraordinary ease, and on reduction is converted into di- and tetrahydro-derivatives Pyrazole, which crystallises in long colourless needles, m p 70° and b p 185°, is much more resistant to change

[1] L Claisen, *Ber*, 1903, 36, 3664 [2] R Störmer and Martinsen, *Ann*, 1907, 352, 322

In pyrrole the basic character is barely evident On the other hand pyrazole, although it gives no reaction with litmus and can be removed from weakly acid solutions by a current of steam, nevertheless yields well-defined salts with acids

All the chemical properties of pyrazole show it to be more nearly allied to pyridine and benzene than to pyrrole It exhibits, to an even greater degree than thiophene, those peculiarities which were first observed in the aromatic series and are therefore associated with the term "aromatic character"

A number of facts established by Knorr clearly illustrate the *aromatic character of pyrazole*

1 Fuming sulphuric acid converts pyrazole into a sulphonic acid, which in its reactions shows certain resemblances to the aromatic sulphonic acids

2 In halogen derivatives of pyrazole, a halogen atom attached to the nucleus is even more firmly held than in benzene derivatives

3 When pyrazole is treated with concentrated nitric acid, hydrogen is readily exchanged for a nitro-group Like the aromatic nitro-compounds, 4-nitro-pyrazole and its derivatives can be reduced to amino-compounds[1]

4 Amino-pyrazole resembles the aromatic bases in its behaviour It gives a colour reaction with a solution of bleaching powder, and is readily diazotised

5 Diazo-pyrazoles can be coupled with phenols to form azo-dyes, in exactly the same manner as the aromatic diazo compounds They differ from most of the latter in the stability of their salts in aqueous solution On boiling these solutions there is no visible evolution of nitrogen, this only occurs on prolonged heating at a higher temperature Diazo pyrazoles, however, do not undergo the usual "diazo-reactions"

6 Pyrazolone, or 5-hydroxy-pyrazole, has a pronounced phenolic character

7 Towards oxidising and reducing agents, pyrazole shows the same remarkable stability as benzene

8 Homologues of pyrazole resemble those of benzene in being readily oxidised to the corresponding carboxylic acids

Hence it will be seen that the analogy between pyrazole and benzene is a far-reaching one

The *similarity between pyrazole and pyridine* may also be illustrated by several examples It is clearly shown in the behaviour of the double salts formed by pyrazole with platinic chloride, and in similar double salts given by pyridine and pyrazole with other metallic compounds, such as mercuric chloride, potassium platinous chloride and the sulphates of copper, zinc and cadmium

In smell and other properties the alkyl derivatives of pyrazole so

[1] Knorr, *Ber*, 1895, 28, 715 Knorr and Stolz, *Ann*, 1896, 293, 58

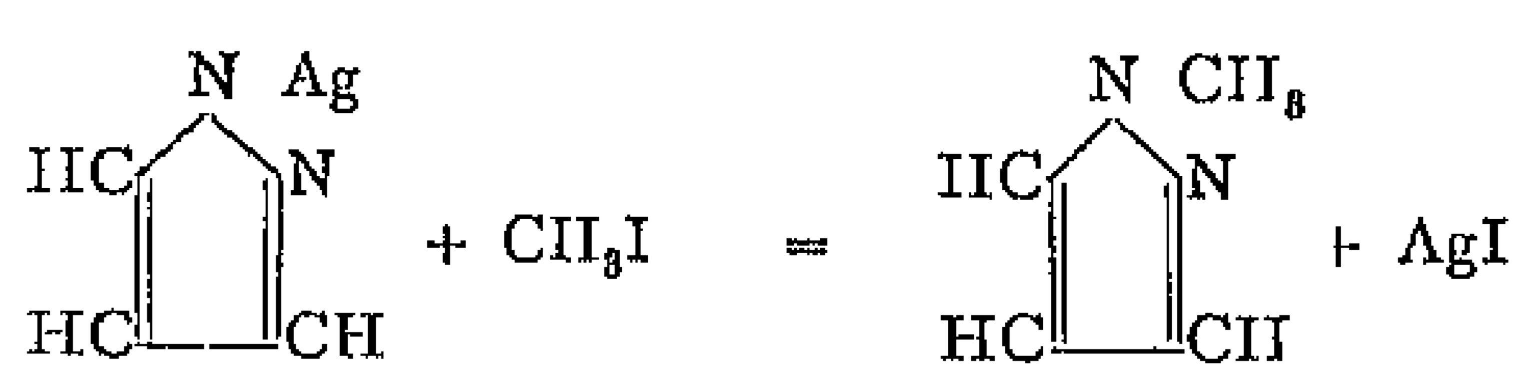
closely resemble pyridine bases that on casual examination they may easily be mistaken for them. The carboxylic acids of pyrazole also possess many points in common with those of pyridine. For example, when polycarboxylic acids of pyridine are heated, they part with carbon dioxide to give the mono-acid, and it is found that the carboxyl group in the α-position to nitrogen is the first to be removed. By a repetition of this process the monocarboxylic acid is converted into pyridine. The properties of 3- (or 5-) pyrazole-carboxylic acid are very closely allied to those of pyridine α-carboxylic acid (see Picolinic Acid).

Owing to the basic character of pyrazole, its resemblance to pyridine is more evident than its resemblance to benzene. Pyrazole is a weak secondary base, as such it may be acetylated, benzoylated, and converted into derivatives of urea and urethane.[1]

It unites with alkyl iodides to form crystalline ammonium compounds. These are of importance in the preparation of homologues of pyrazole, as under the influence of heat the alkyl radical is transferred from nitrogen to a carbon atom of the nucleus. The Hofmann synthesis of aniline homologues (p. 380) can therefore be applied to the pyrazole series. As will be seen later, this reaction is also of value in the pyridine group.

A *separation of the secondary and tertiary pyrazole-bases* resulting from the above process may be effected by taking advantage of the fact that secondary pyrazoles can be quantitatively thrown out of an aqueous solution in the form of their silver salts, tertiary pyrazoles remaining unchanged.

The silver compounds are readily formed by all pyrazoles containing a free imino-hydrogen atom, and are useful for the preparation of N-alkyl substituted derivatives by double decomposition with alkyl iodides. Thus silver pyrazole and methyl iodide yield 1-methyl-pyrazole.



According to Knorr, these *N-alkyl-pyrazoles* are better prepared by distilling the corresponding pyrazole alkiodides.

An interesting regularity has been observed in connection with the physical constants of pyrazole homologues.[2] Symmetrically constituted compounds possess higher melting points than the isomeric unsymmetrical compounds, and of the latter the tertiary derivatives melt much lower than the isomeric secondary bases.

For example	Melting point	Boiling point
3 5-Dimethyl-pyrazole (symm.)	107°	220°
3 4-Dimethyl-pyrazole (unsymm., second.)	57° to 59°	222°
1 3-Dimethyl-pyrazole (unsymm., tert.)	liquid	140° to 141°

[1] Knorr, *Ber.*, 1895, 28, 716. [2] For further details, see Knorr, *Ber.*, 1895, 28, 694.

A further difference between C alkyl and N alkyl derivatives is that the former usually have only a slight odour, while the latter generally have a strong smell recalling that of pyridine

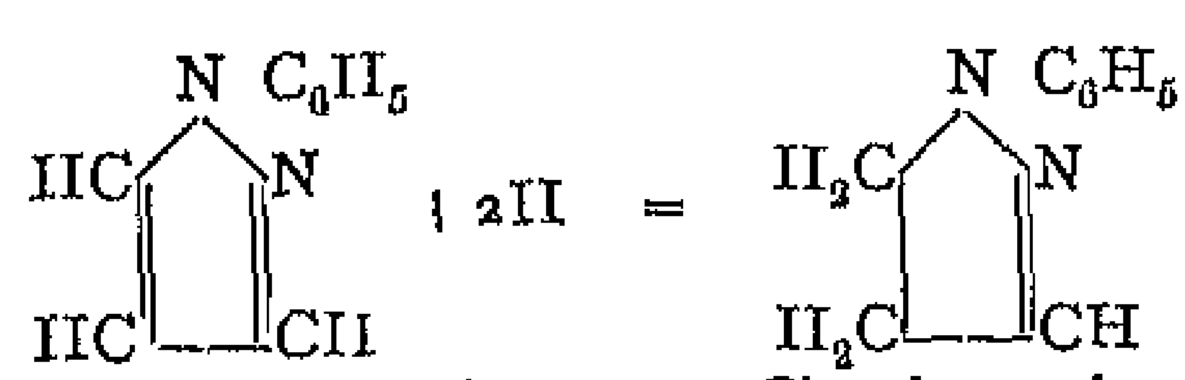
It has already been mentioned that the pyrazole nucleus is stable towards oxidising agents The alkyl groups attached to the ring in homologues of pyrazole may be successively oxidised to carboxyl groups by use of potassium permanganate

In 1-phenyl-pyrazoles the benzene nucleus is more readily oxidised away than the pyrazole nucleus, as is shown by the formation of pyrazole when 1-phenyl-pyrazole is oxidised with permanganate in sulphuric acid solution (Knorr) As in the aromatic series, the benzene ring is still more easily disrupted if its stability is first lowered by the introduction of an amino or hydroxyl group For example, the benzene ring of 1-aminophenyl-3-methyl-pyrazole is much more readily attacked than that of 1-phenyl-3-methyl-pyrazole A remarkable point is the stability of pyrazole derivatives under these conditions as compared with corresponding derivatives of pyrrole, the latter being completely oxidised by potassium permanganate

The action of nascent hydrogen (from sodium and alcohol) varies with different compounds of the pyrazole group

Pyrazole itself and its homologues are apparently not attacked by sodium and alcohol

1-Phenyl-pyrazole and its homologues, *i e*, those derivatives formed by the interaction of phenyl-hydrazine and β-diketo-compounds, have been shown by Knorr to be reduced to pyrazoline derivatives



1-Phenyl-pyrazole 1 Phenyl-pyrazoline

Pyrazoline bases obtained from phenyl-hydrazine are changed by oxidising agents, such as chromic acid, nitrous acid, ferric chloride, and hydrogen peroxide, into characteristic dyes varying from red to blue in colour This reaction, described by Knorr as the **pyrazoline reaction**, may be used for the detection of pyrazole and pyrazoline bases derived from phenyl-hydrazine

The reaction is conveniently carried out as follows A small amount of the pyrazole base is dissolved in alcohol in a test tube, and a small piece of sodium added to the boiling solution After the metal has dissolved, the mixture is diluted with water, the alcohol distilled off, and the pyrazoline base extracted from the residue by means of ether After removing the ether, the base is dissolved in comparatively strong sulphuric acid and a drop of a solution of sodium nitrite or potassium dichromate added, when a fine coloration (red to blue) is produced

Pyrazoline and its Derivatives.—Pyrazoline derivatives differ considerably in their properties from those of pyrazole, owing to their much lower stability. This is another indication of the aromatic nature of pyrazole, since it is almost a characteristic of aromatic compounds that the addition of two hydrogen atoms to the ring results in diminished stability.

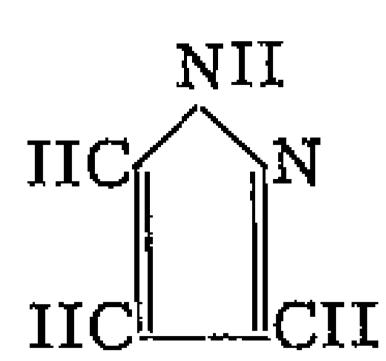
The pyrazolines give the reactions of aliphatic derivatives, resembling unsaturated compounds in their behaviour towards permanganate and nascent hydrogen. They resemble hydrazones in the manner in which they are hydrolysed by mineral acids, and aldazines in their decomposition into gaseous nitrogen and nitrogen-free substances. The presence of a five-membered ring is only revealed in the ease with which pyrazolines are converted into pyrazoles.

Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. The parent substance, **pyrazoline**, an oil of boiling-point 144°, is the most stable of all these compounds.

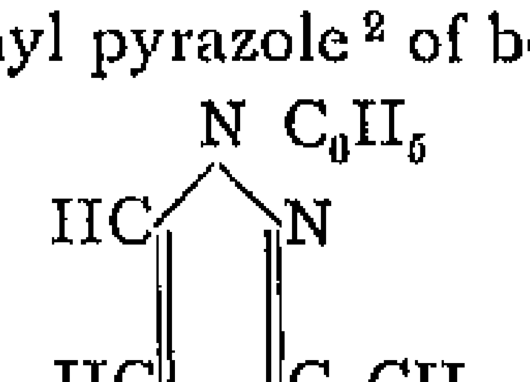
The *pyrazolidines*, or completely reduced pyrazoles, have not been thoroughly investigated owing to their instability. They possess strong reducing properties and readily give up hydrogen to form pyrazolines.

Derivatives of Pyrazole—Tautomerism in the Pyrazole Series.

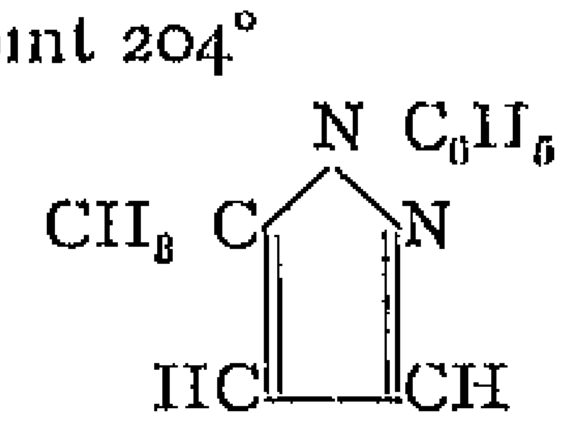
As the result of an investigation into the synthetic derivatives of 1-phenyl-pyrazole,[1] Knorr assigned to the then unknown pyrazole the following constitution:—



The problem of the structure of pyrazole entered a new phase in 1893, when Knorr and Macdonald showed that the oxidation of the well-known isomeric compounds 1-phenyl-3-methyl-pyrazole and 1-phenyl-5-methyl-pyrazole, or their amino-derivatives, gave one and the same methyl pyrazole[2] of boiling-point 204°.



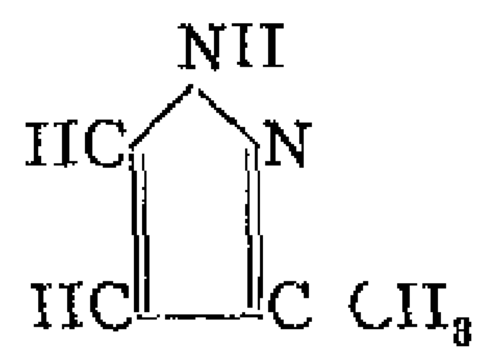
1-Phenyl-3-methyl-pyrazole
Crystalline, m.p. 37°
B.p. 254° to 255°
Methiodide, m.p. 144°



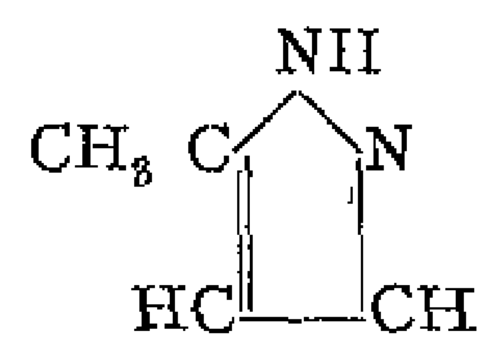
1-Phenyl-5-methyl-pyrazole
Colourless oil, b.p. 254° to 255°
Does not solidify at −20°
Methiodide, m.p. 296°

[1] *Ber.*, 1890, 23, 1103. [2] Knorr and Macdonald, *Ann.*, 1894, 279, 188. For isomerism in the pyrazole series, see also K. von Auwers, *Ber.*, 1922, 55, 3880; 1925, 58, 528; 1927, 60, 1730.

By this method it is therefore not possible to obtain the two methyl-pyrazoles of the formulæ



and



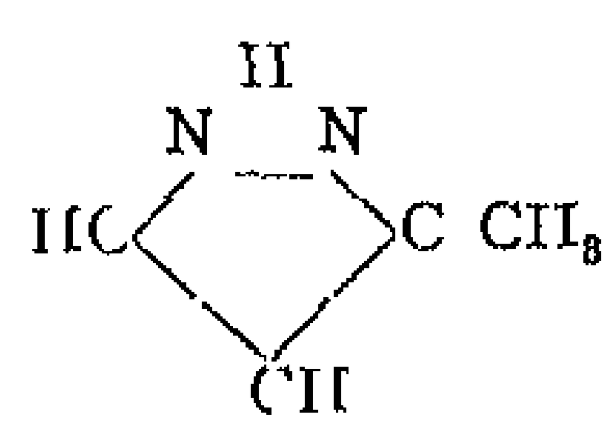
corresponding to the above phenyl-methyl-pyrazoles.

Knorr and Macdonald also failed to observe the production of isomeric methyl-pyrazoles on condensing hydrazine hydrate with oxymethylene-acetone. On the other hand, Claisen and Roosen found that phenyl-hydrazine reacted with oxymethylene-acetone to form two isomeric phenyl-methyl-pyrazoles.[1]

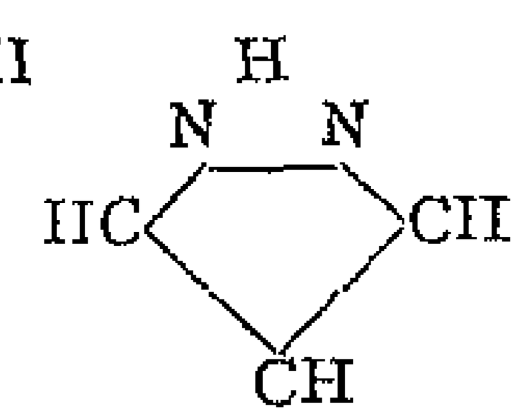
Hence it appeared that positions 3 and 5 in pyrazole were equivalent to one another. *Methyl pyrazole*, b.p. 204°, may therefore be a mixture of the two desmotropic forms, 3-methyl-pyrazole and 5-methyl-pyrazole, in a state of continuous and rapid interconversion.

For these reasons Knorr described the compound as 3 (5)-methyl-pyrazole and formulated it as I below.

I



II

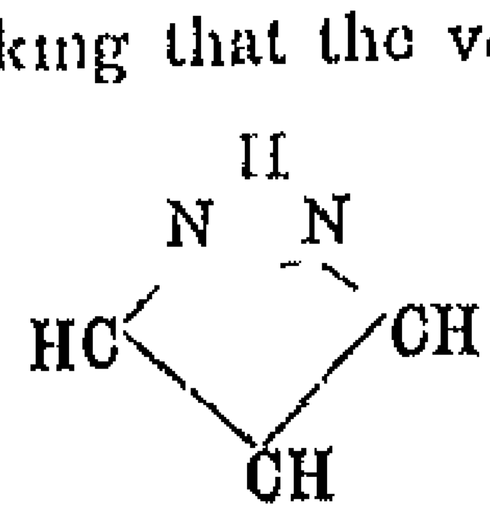


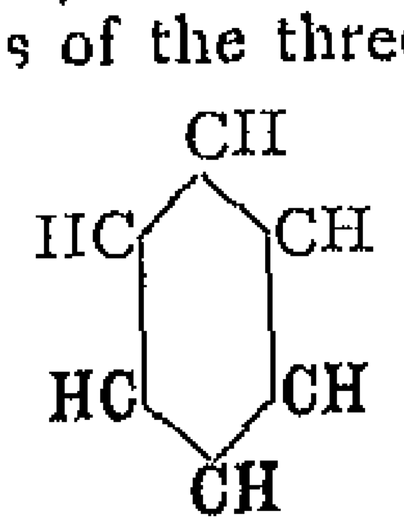
The accuracy of this conclusion was confirmed by the discovery that methyl-pyrazole could react simultaneously in the sense of a 3- and a 5-methyl-pyrazole.

It is therefore assumed that the 1-hydrogen atom in pyrazole is not permanently attached to a given nitrogen atom, but is linked sometimes to one and sometimes to the other, with corresponding readjustment of the double bonds, as indicated in formula II.

This state of affairs, as revealed by experimental investigation, is of particular interest because it appears to throw some light on the constitution of benzene, a problem which is less easily attacked from the experimental side.

It is quite permissible to apply the experience gained with pyrazole to the case of benzene, since the similarity between these compounds is so striking that the valency conditions of the three methine groups



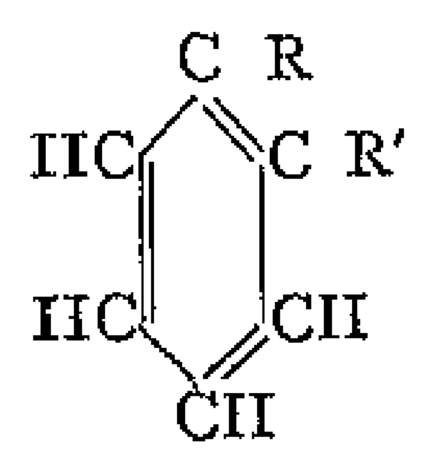
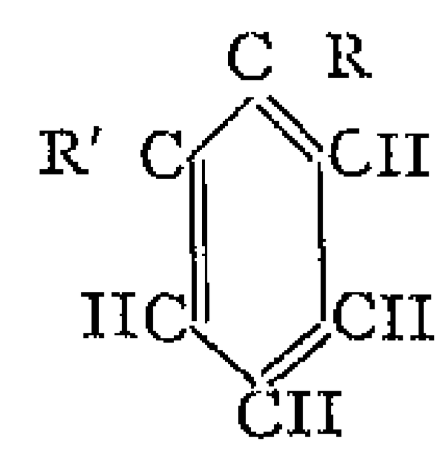


[1] *Ber.*, 1891, **24**, 1888; *Ann.*, 1894, **278**, 361.

of pyrazole must be practically the same as those of the three methine groups in a half of the benzene molecule [1]

From this point of view Knorr supports Kekulé's formula for benzene

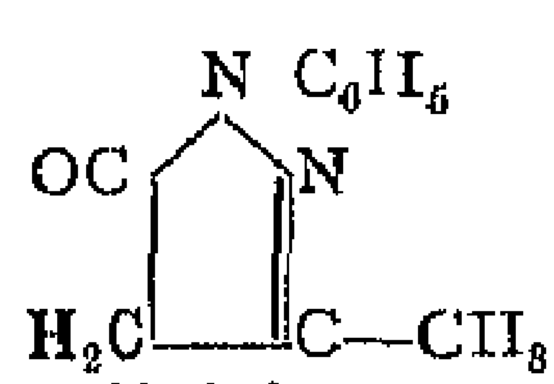
The identity of the 1 2- and 1 6-disubstitution products of benzene, which has been used as an argument against the Kekulé formula (see p 356), is readily understood from our knowledge of pyrazole The rearrangement of the double bonds in benzene must occur all the more easily since there is here no question of the hydrogen atoms changing position, whereas in pyrazole the alteration of valency bonds is accompanied by an actual displacement of the 1-hydrogen atom Hence the lack of any evidence pointing to the separate existence of the two forms,

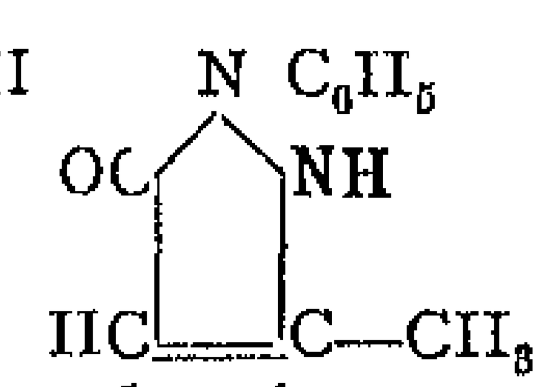



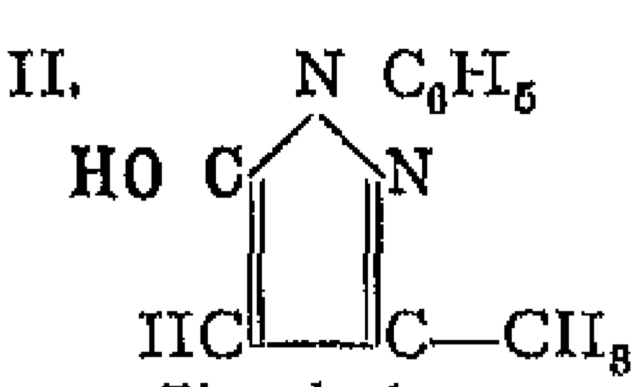
is due to the fact that they are desmotropic modifications, which undergo transformation into one another with extraordinary ease

In addition to the above tautomerism of 3-(5) methyl-pyrazole, a second and very peculiar type of tautomerism has been observed in the pyrazole series in connection with **1-phenyl-3-methyl 5-pyrazolone**, the parent compound of antipyrine, which is usually formulated as I It is prepared in large quantities as an intermediate product in the manufacture of antipyrine, by condensing acetoacetic ester with phenyl-hydrazine (see p 261)

According to Knorr,[2] this extremely reactive compound may react simultaneously in the three desmotropic forms

I 
Methylene form

II 
Imine form

III. 
Phenolic form

In this case we are therefore dealing with a very complicated case of tautomerism, described by Knorr as "double tautomerism"

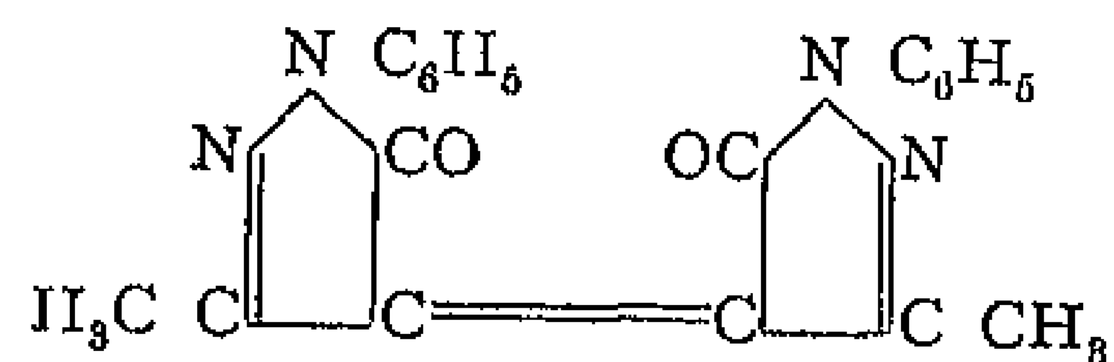
1-Phenyl-3-methyl-5-pyrazolone itself is known only in one form Whether prepared by synthesis or from a derivative corresponding to one or other of the above three types, it is always obtained in the form of a substance of melting-point 127°, crystallising in white prisms Which of the above three formulæ represents this compound has not

[1] Knorr, *Ann*, 1893, 278, 195 [2] Knorr, *Ber*, 1895, 28, 706

yet been established with certainty, but numerous derivatives are known corresponding to each type

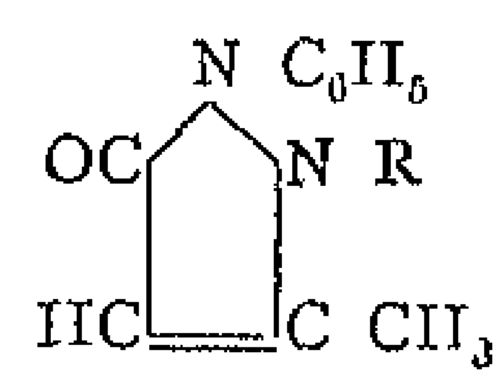
The majority of the derivatives of phenyl-methyl-pyrazolone possess the *methylene structure*

Examples of this type are 1-*phenyl*-3-*methyl*-4-*dimethyl-pyrazolone* and *pyrazole blue* The latter is readily obtained by gentle oxidation of phenyl-methyl-pyrazolone, and represents the indigo of the pyrazole series



Pyrazole blue

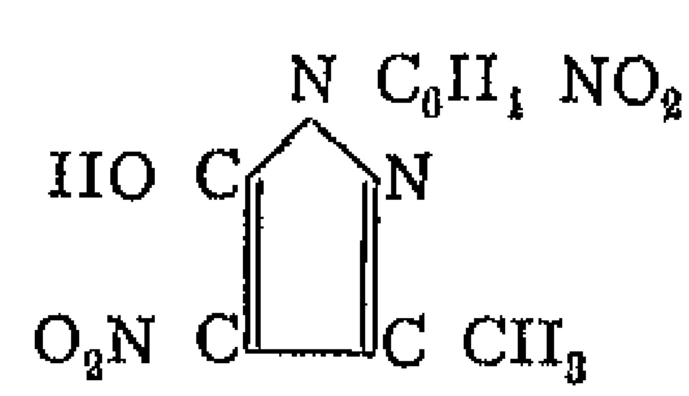
The *imine structure* is only found in the particular group of phenyl-methyl-pyrazolone derivatives known as *antipyrines*



Proof of the imine structure of antipyrines is found in the disruption of antipyrine by means of sodium and carbon dioxide, to give the anilide of β-methylamino-crotonic acid [1]

Three other groups of compounds must be considered as belonging to the *phenolic type*, viz, the *phenol-ethers*, *esters* and *salts* of *phenyl-methyl-pyrazolone*

In conclusion, it may be mentioned that certain nitro-derivatives of phenyl-methyl-pyrazolone, such as 4-*nitro*-1-*p*-*nitrophenyl*-3-*methyl-pyrazolone*, known as **picrolonic acid**,



are also regarded by Knorr as nitrophenols, owing to their similarity to picric acid Picrolonic acid yields very sparingly soluble salts, which in their properties show a close resemblance to the picrates They are usually even less soluble than the latter, and may be employed with advantage for the isolation and identification of bases

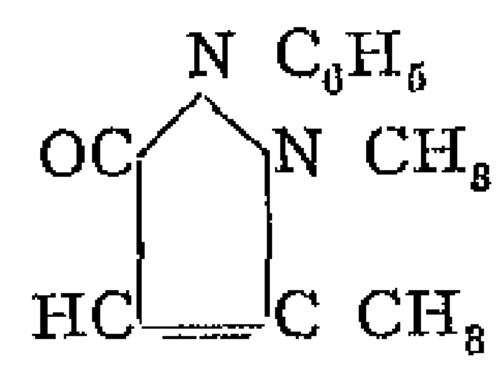
The arguments which lend support to each of the three competing formulæ of phenyl-methyl-pyrazolone lead to the conclusion that the

[1] Knorr and Taufkirch, *Ber*, 1892, 25, 768

acidic hydrogen atom and the double bonds occupy no fixed positions in this compound It is the peculiar mobility of this hydrogen atom which enables tautomeric changes to be completed with such ease

Analogous rearrangements of bonds, but without any movement of hydrogen, are also shown by antipyrine in certain addition reactions

Antipyrine, 1-*phenyl*-2 3-*dimethyl*-5-*pyrazolone*,

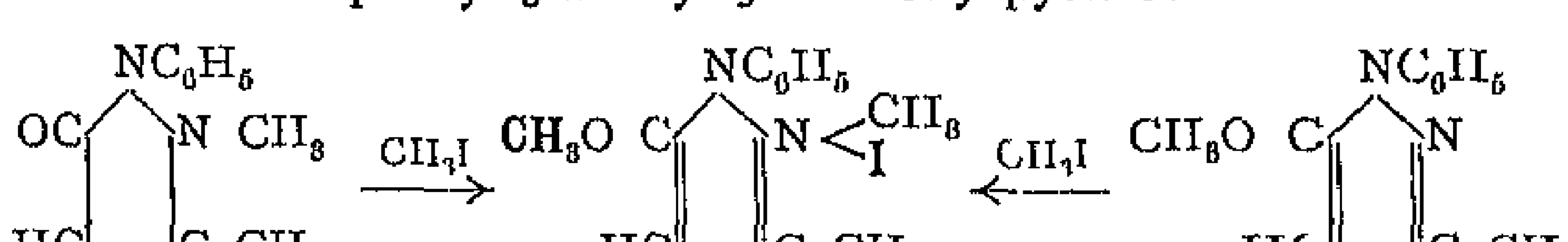


is the most important member of the pyrazole group, and is used extensively in medicine as a febrifuge It is prepared industrially by heating 1-phenyl-3-methyl-5 pyrazolone with methyl iodide and methyl alcohol at 100° under pressure, the hydriodide of antipyrine is thus produced, from which sodium hydroxide liberates antipyrine itself A method of preparing antipyrine which throws light upon its constitution consists in the condensation of acetoacetic ester with symmetrical phenyl-methyl-hydrazine

It crystallises in white plates, m p 113°, and dissolves readily in water and alcohol The aqueous solution is coloured red by ferric chloride, and green by nitrous acid Antipyrine is a strong monacid base and readily forms salts, most of which are easily soluble in water

At ordinary temperatures alkyl iodides unite with antipyrine in the same manner as with the inner salts of phenol-ammonium bases, *i e phenol betaines*, in that iodine attaches itself to the 2-nitrogen atom of antipyrine, while the alkyl group unites with the oxygen atom This behaviour originally led to the suggestion that antipyrines should be formulated as phenol-betaines

From antipyrine and methyl iodide, for example, there is formed an antipyrine "*pseudo*"-methiodide,[1] which is identical with the methiodide of 1-phenyl-3-methyl-5-methoxy-pyrazole

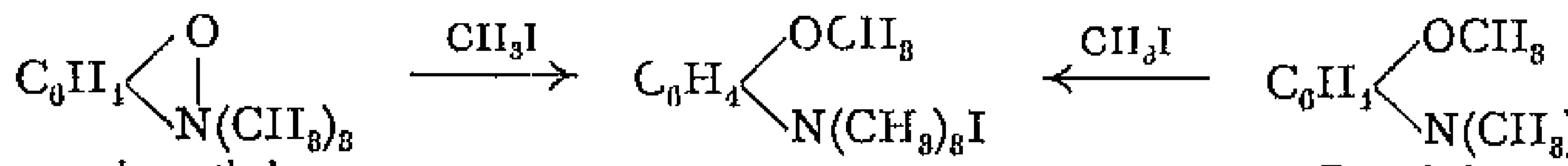


Antipyrine — Antipyrine *pseudo* methiodide — 1-Phenyl 3 methyl 5 methoxy pyrazole

Phenol betaines unite with methyl iodide in a similar way, in the

[1] Knorr terms these compounds antipyrine *pseudo* methiodides, in order to indicate their derivation from antipyrine, the term antipyrine methiodide being reserved for the as yet unknown true methiodide It was the formation of these *pseudo* compounds which first led Knorr to consider whether antipyrine might not be more correctly formulated as a phenol betaine, *i e*, the inner salt of a phenol ammonium base Compare also Michaelis, *Ann*, 1902, **320**, 45, 1904, **331**, 197

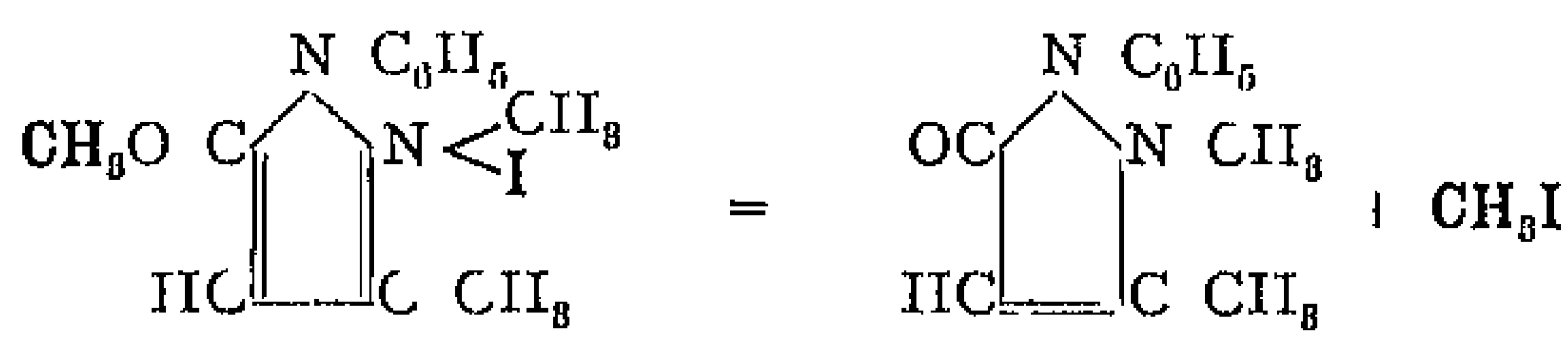
presence of caustic potash The resulting quaternary iodides are identical with those obtained from the dimethylamino-anisoles



o-Trimethyl-ammonium phenoxide   *o*-Dimethylamino-anisole

A detailed comparison of antipyrine with *o*-trimethyl-ammonium phenoxide, however, revealed the fact that, apart from the addition of alkyl iodide, these compounds were quite different in behaviour, the *pseudo*-alkiodides of both compounds had also different properties, and hence the "phenol betaine" formula for antipyrine was rejected

On being fused, the pseudo-alkiodides of antipyrine do not break up, as might be expected, into alkyl iodide and a phenolic ether, but into alkyl iodide and antipyrine



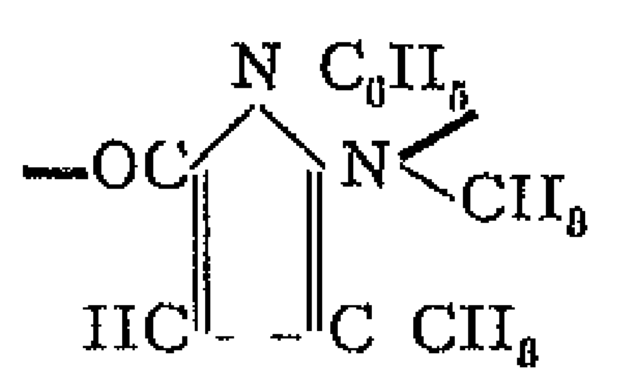
Antipyrine is also regenerated from the pseudo-methiodide by the action of alkalis, slowly in the cold and more rapidly on heating[1]

In the above reactions it will be seen that antipyrine behaves as an unsaturated compound of type I

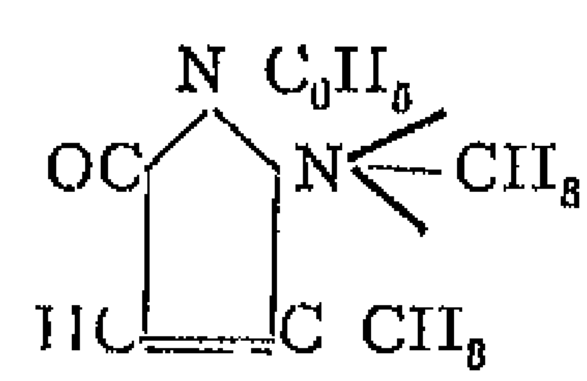
Under the influence of alkalis at higher temperature, however, antipyrine and similarly constituted compounds react as unsaturated substances[2] according to formulæ II and III

Finally, on interaction with bromine, antipyrine behaves in the sense of formula IV

I

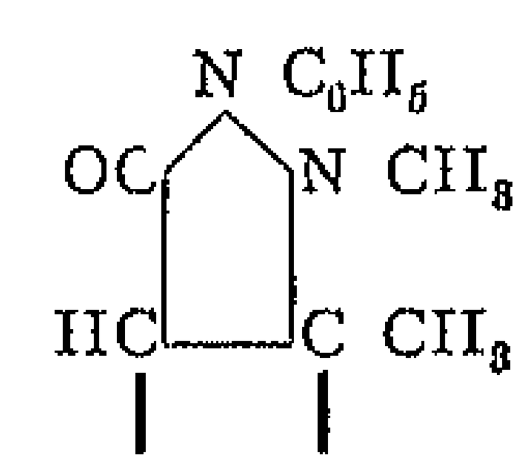


II



III

IV



[1] An equally remarkable behaviour towards alkyl iodides, resembling the above case of antipyrine, is shown by the γ-quinolones and by nitroso dimethylaniline (Knorr, *Ber*, 1897, 30, 922, 933) All these reactions involve addition to the ends of a long chain containing neighbouring double bonds, which leads to a simultaneous rearrangement of the bonds They thus recall the cases of 1 4-addition studied by Thiele (p 23) [2] Knorr, *Ann*, 1896, 293, 7

This remarkable variation in addition-reactions is explained by Knorr as being due to intramolecular movements of the hydrogen atom in antipyrine, accompanied by changes of linking[1]

It is suggested that the 2-nitrogen atom alternates between the tri- and pentavalent states, thus permitting displacements of valency bonds similar to those assumed in the case of tautomeric compounds

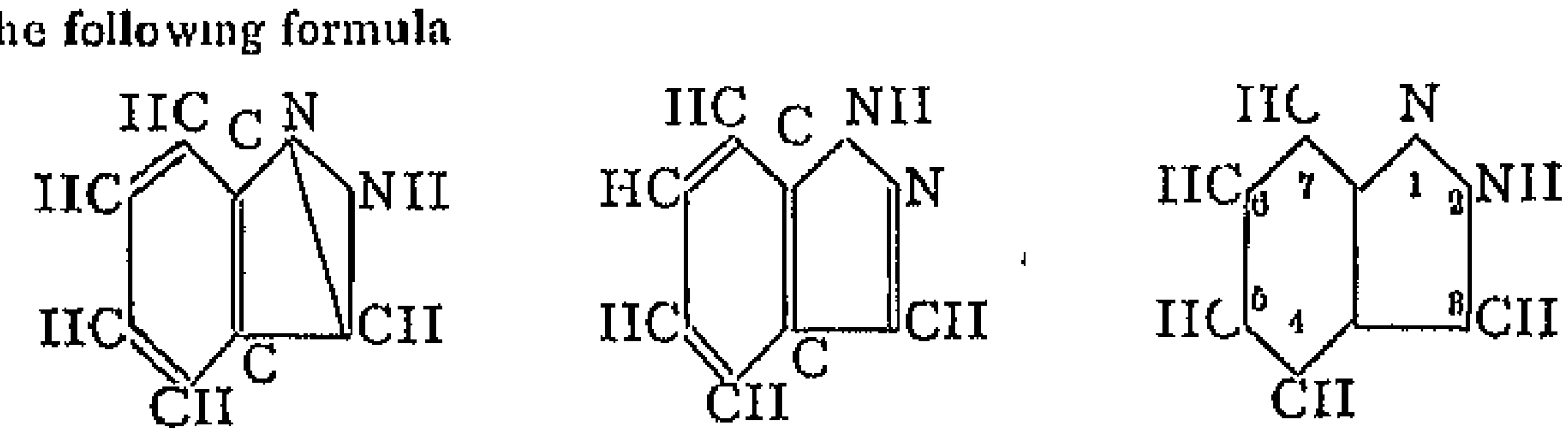
Among the great number of antipyrine molecules present in solution or the fused state, there will always be some in which the valency conditions correspond to the above four types

In the addition of alkyl halides in the cold, and in the production of antipyrine salts, form I will react in preference, since the negative radical will naturally attach itself to the basic and the positive radical to the acidic point of the antipyrine molecule Only at higher temperatures, at which the alkiodides of the phenol-ether type are no longer capable of existence, does antipyrine react with methyl iodide according to formulæ II and III Bromine, on the other hand, unites in positions 3 and 4 (Form IV), in accordance with its tendency to add on to a double carbon linkage

Certain other derivatives of this type are of importance, *e g* **salipyrine**, or antipyrine salicylate, **tolypyrine** or *p*-tolyl-dimethyl-pyrazolone, and **pyramidone** or 4-dimethylamino-antipyrine These and other derivatives are employed medicinally, particularly as substitutes for antipyrine

Indazoles or Benzo-pyrazoles

The ring system of the indazoles consists of a condensed benzene pyrazole nucleus, and these compounds thus stand in the same relationship to the pyrazoles as the indoles to the pyrroles Here also it is found that the hydrogen atom linked to nitrogen is mobile, and that one parent substance consequently gives rise to several series of derivatives, as in the pyrazole group The *indazoles* are referred to indazole, discovered by Fischer and Tafel, and the *isindazoles* to the hypothetical isindazole The position of substituents is indicated by numbers, as in the following formula



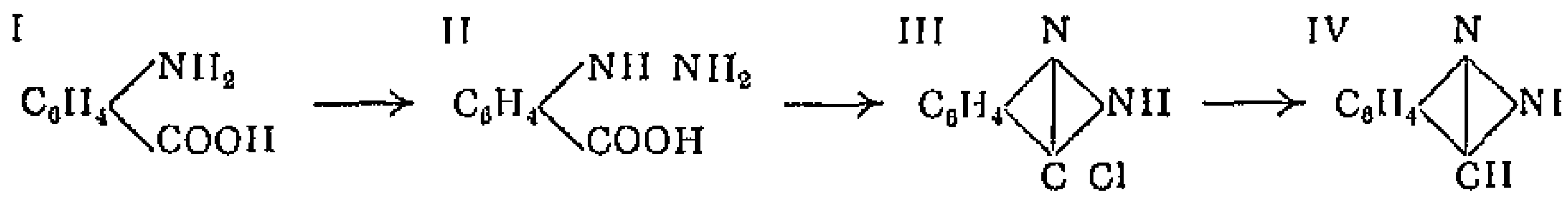
Indazole Isindazole

Opinion is still divided as to whether indazole actually corresponds to the above formula, containing a meta linking between carbon and nitrogen[2]

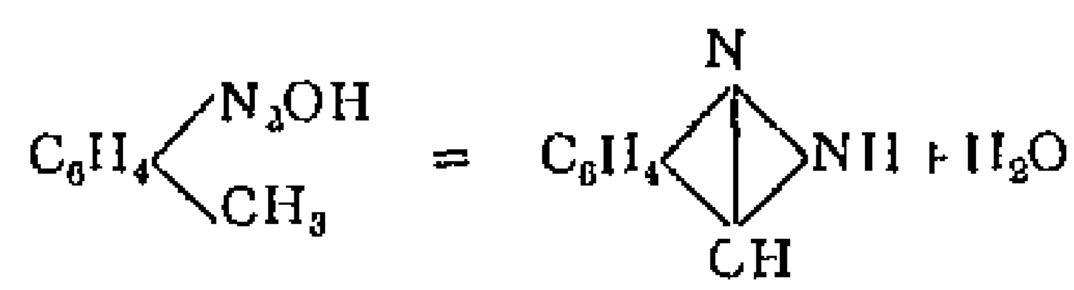
Indazole is a crystalline compound, m p 146° and b p 270°, which is best prepared from anthranilic acid (I) The latter may be diazotised and reduced to o *hydrazino benzoic acid* (II), which, on heating with phosphorus oxychloride, yields chloro

[1] *Ann*, 1896, 293, 39 [2] Compare, for example, Hantzsch, *Ber*, 1902, 35, 892

indazole (III) This on reduction with zinc dust and hydrochloric acid[1] gives indazole (IV)



It is also obtained by removing the elements of water from *o* toluene diazo hydroxide in neutral solution

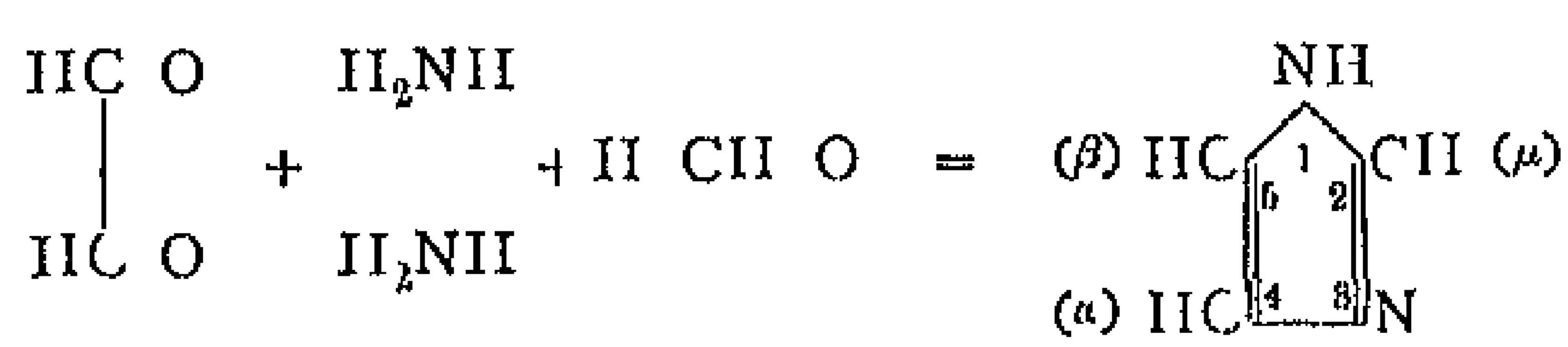


A large number of indazoles substituted in the benzene nucleus have been prepared by this method, by starting from substituted *o* toluene diazo hydroxides The diazo compounds prepared from nitrated and brominated *o* toluidines have a strong tendency to form rings of this type

II—IMINAZOLE OR GLYOXALINE GROUP

The ring system of the iminazoles, like that of the pyrazoles, consists of three carbon and two nitrogen atoms In this case, however, the latter are not adjacent but are separated by a carbon atom Hence iminazoles may be regarded as cyclic amidines, derived from the complex $HN{=}CH{-}NH_2$

Iminazole, the parent compound of the series, is formed, as described on p 247, by the action of ammonia on glyoxal, and hence is also known as **glyoxaline** In this reaction it is assumed that a part of the glyoxal is first broken up to give formic acid and formaldehyde, and that the latter then condenses with the ammonia and glyoxal



Glyoxaline

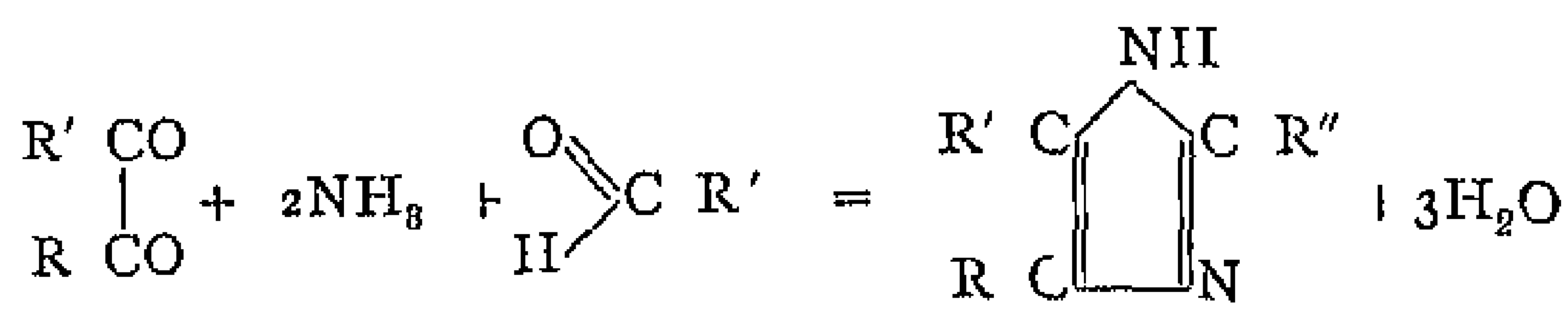
The figures or letters attached to the formula indicate the manner in which substituents are represented

The above is a somewhat troublesome method of preparing glyoxaline, and it is more convenient to allow formaldehyde and excess of ammonia to interact with dinitro-tartaric acid, when a good yield of ammonium glyoxaline-dicarboxylate is obtained, from which by addition of hydrochloric acid free *glyoxaline-dicarboxylic acid* is precipitated On heating this to about 300° it decomposes smoothly into carbon dioxide and glyoxaline

Glyoxaline forms prisms, m p 88° to 89° and b p 255° It is a weak base, and when warm possesses a faint fishy smell

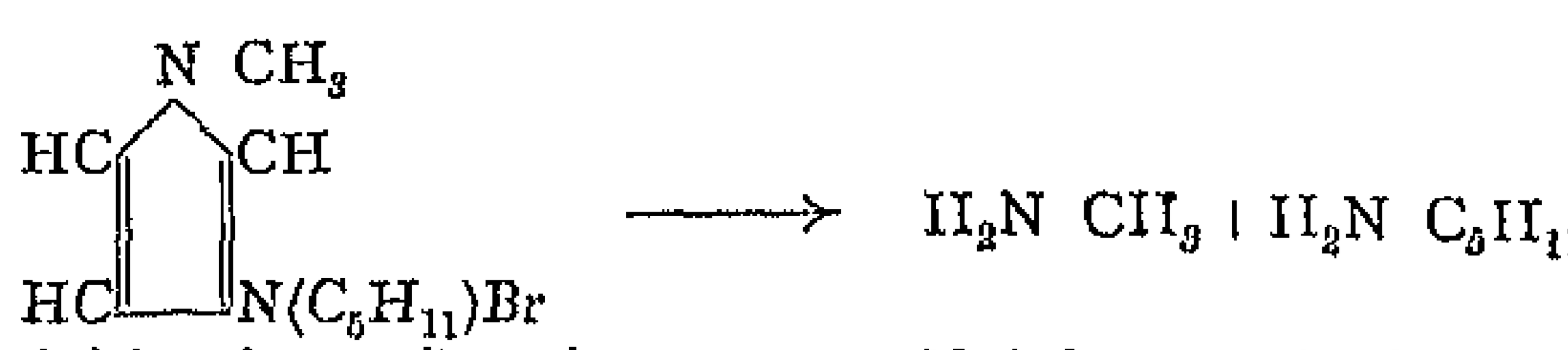
[1] E Fischer and Seuffert, *Ber*, 1901, 34, 795

Substituted glyoxalines are prepared by a method analogous to that employed for glyoxaline, by the action of ammonia and aldehydes on glyoxal or other 1 2-diketo compounds



Properties of the Glyoxalines—Glyoxalines are stronger bases than the isomeric pyrazoles, as may be seen from their basic constants (glyoxaline $1\ 2 \times 10^{-7}$, pyrazole $3\ 0 \times 10^{-12}$)

The imino-hydrogen atom of glyoxaline can be replaced by metals and alkyl radicals Ammoniacal silver solutions yield with glyoxaline a flocculent precipitate of the silver salt, which is only slightly soluble in excess of ammonia The parent glyoxaline bases are quite stable towards alkalis, but this property is lost in the methiodides and similar derivatives, which on heating with alkalis decompose into a mixture of two primary bases,[1] *e g*,



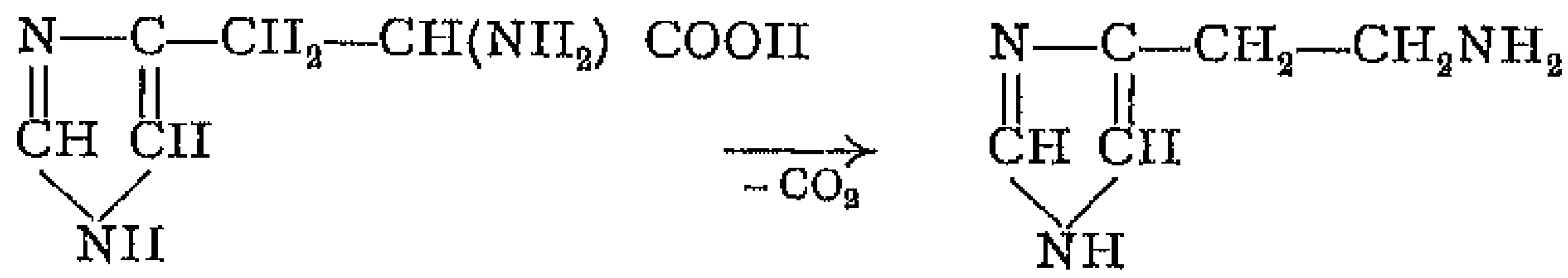
Methylglyoxaline amylbromide Methylamine Amylamine

Glyoxaline and its simple substitution products in which the imino-group is still intact are very readily disrupted, even at 0°, by a mixture of benzoyl chloride and caustic soda, with the production of a carboxylic acid and a dibenzoylated base[2] Benzene diazo-chloride also reacts with glyoxalines containing a free imino-hydrogen atom, to yield coloured diazo-amino-compounds[3]

Occurrence of Glyoxalines in Nature—It has been shown by Pinner that the alkaloid *pilocarpine*, present in jaborandi leaves (of *Pilocarpus pennatifolius*), is a derivative of N-methyl-glyoxaline Other naturally occurring iminazole derivatives, such as caffeine, theobromine and theophylline, have already been described under the purine group The purines, in fact, contain a nucleus formed by the fusion of an iminazole ring with a pyrimidine ring Iminazole derivatives are also met with among the disruption products of proteins (see Histidine) The discovery of a remarkable transformation from the sugars to the iminazole group (see p 303) lends additional interest to this series from the physiological as well as the chemical standpoint

[1] Pinner and Schwarz, *Ber*, 1902, **35**, 2441 [2] According to recent investigations of Oddo and Mingoia (*Gazzetta*, 1926, **56**, 958) this statement is incorrect, the product of the reaction being benzoyl-glyoxaline [3] Burian, *Ber*, 1904, **37**, 696

β-Iminazyl-ethylamine, *histamine*, is of biochemical interest. It is formed from histidine by bacterial putrefaction, and can therefore be isolated from the putrefaction products of proteins



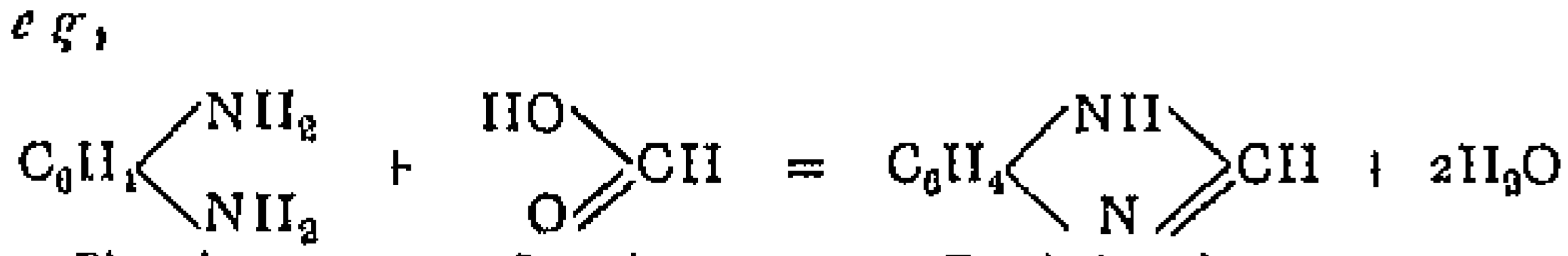
Histidine Histamine

It is found in the fresh mucous membrane of the small intestine, and is also present in preparations of ergot, where it is of importance in connection with the activity of the drug, as it causes contraction of the muscles of the uterus. The base has been prepared synthetically.[1] Its hydrochloride crystallises from alcohol in prisms, melting at 240° with decomposition.

4(5)-Nitro iminazole 5(4) carboxylic acid has been obtained by the oxidative disruption of protein by means of nitric acid. It is readily prepared in the following stages: 4(5)-*methyl-iminazole* → 5(4)-*nitro*-4(5)-*methyl-iminazole* → *carboxylic acid*.[2]

Benziminazoles or Benzo-glyoxalines

These compounds contain a condensed glyoxaline benzene structure, and bear to the glyoxalines the same relationship as the indoles to the pyrroles. They are cyclic *o* amidines of the benzene series, and are formed by the condensation of *o* phenylene diamine and its substitution products with carboxylic acids or their anhydrides, *e g*,



o Phenylene diamine Formic acid Benziminazole

Benziminazole, *o phenylene formamidine*, is obtained by the above method and also by the interaction of chloroform, potassium hydroxide, and *o* phenylene diamine. It crystallises in white needles of melting point 170°.

The basic character of the benziminazoles is not quite so marked as that of the glyoxalines. They are also weakly acidic and generally soluble in aqueous alkalis with the formation of N metallic compounds. Like the glyoxalines they are attacked by benzoyl chloride and caustic soda, yielding dibenzoylated *o* diamines. Towards oxidising and reducing agents they are very stable.

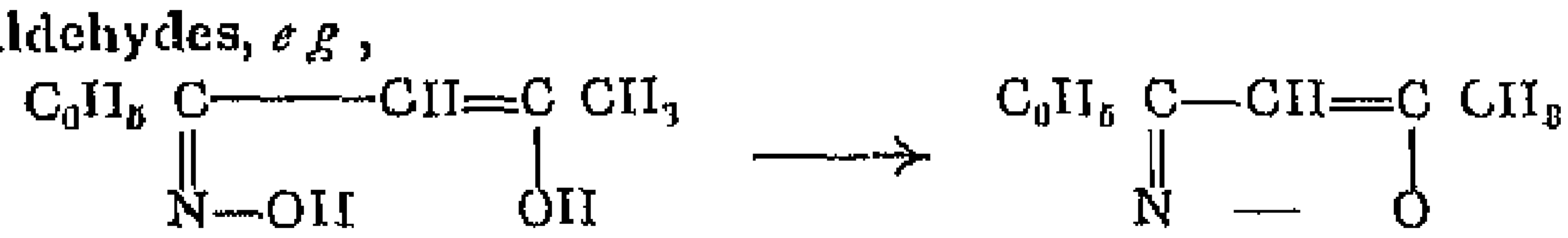
III.—ISOXAZOLES, OXAZOLES AND THIAZOLES

In those rings composed of three carbon atoms linked with one nitrogen and one oxygen atom, nitrogen and oxygen may be adjacent or separated by an atom of carbon. In the former case the compounds are termed *isoxazoles* and in the latter *oxazoles*.

[1] *Ber*, 1907, 40, 3691. Windaus and Opitz, *Ber*, 1911, 44, 1721. [2] A. Windaus and W. Langenbeck, *Ber*, 1923, 56, 683.

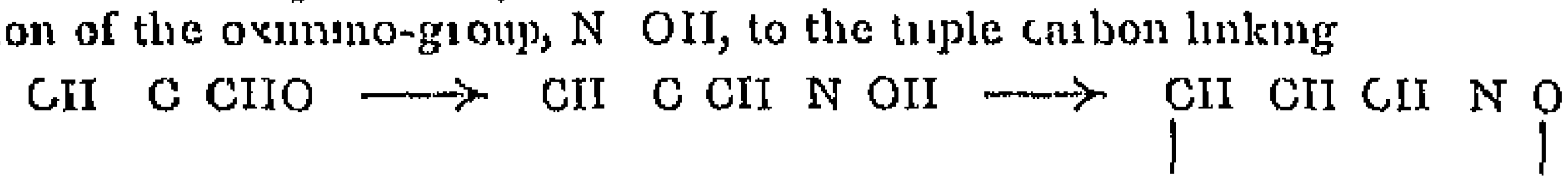
Isoxazole Oxazole

Isoxazoles correspond to pyrazoles, and just as the latter are obtained from hydrazones, the former result by loss of water from the monoximes of β diketones and β ketoaldehydes, *e g*,



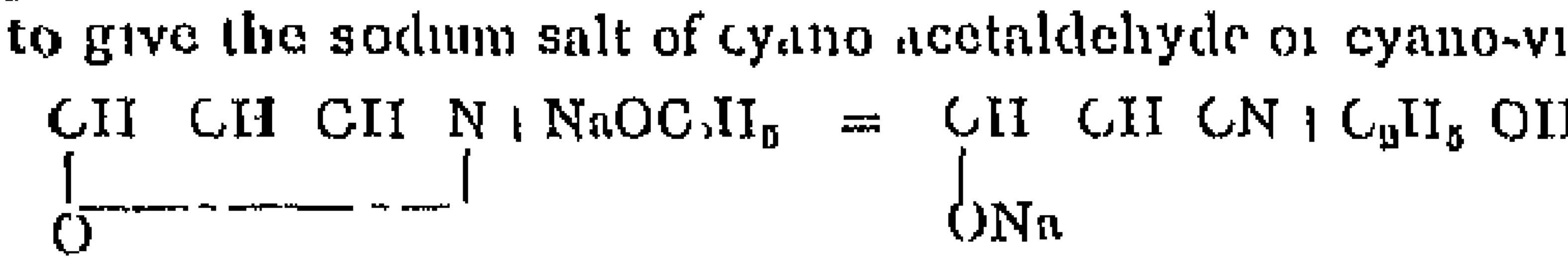
Monoxime of *aci* benzoyl acetone Phenyl methyl isoxazole

They are also produced by the action of red fuming nitric acid on diketones and esters of ketonic acids [1] The parent compound of this group, **isoxazole**, is obtained by the interaction of hydroxylamine and propargylic aldehyde Assuming that an oxime is first produced, this reaction may be considered as an intramolecular addition of the oximino-group, N OH, to the triple carbon linking

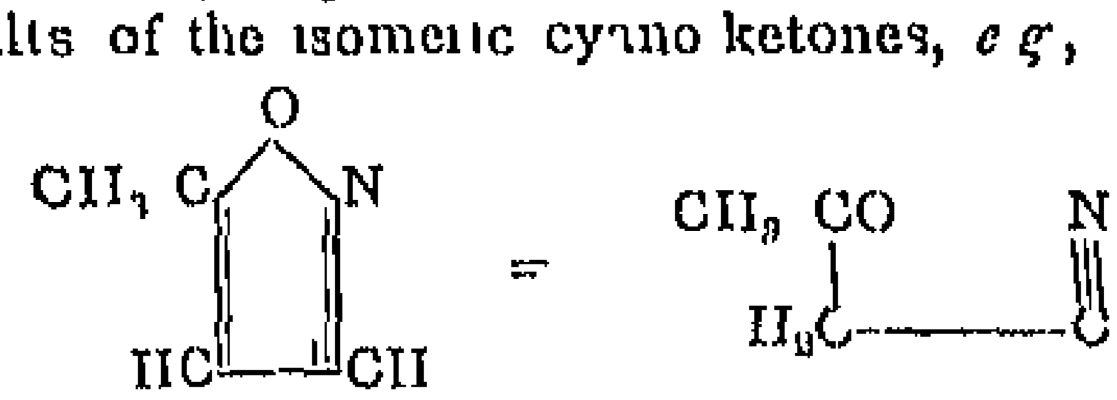


Isoxazole is a clear, mobile liquid, with a penetrating smell resembling that of pyridine, it boils at 95 5° Isoxazoles, like pyrazoles, are weak bases

On being mixed with an alcoholic solution of sodium ethoxide, isoxazole decomposes to give the sodium salt of cyano acetaldehyde or cyano-vinyl alcohol

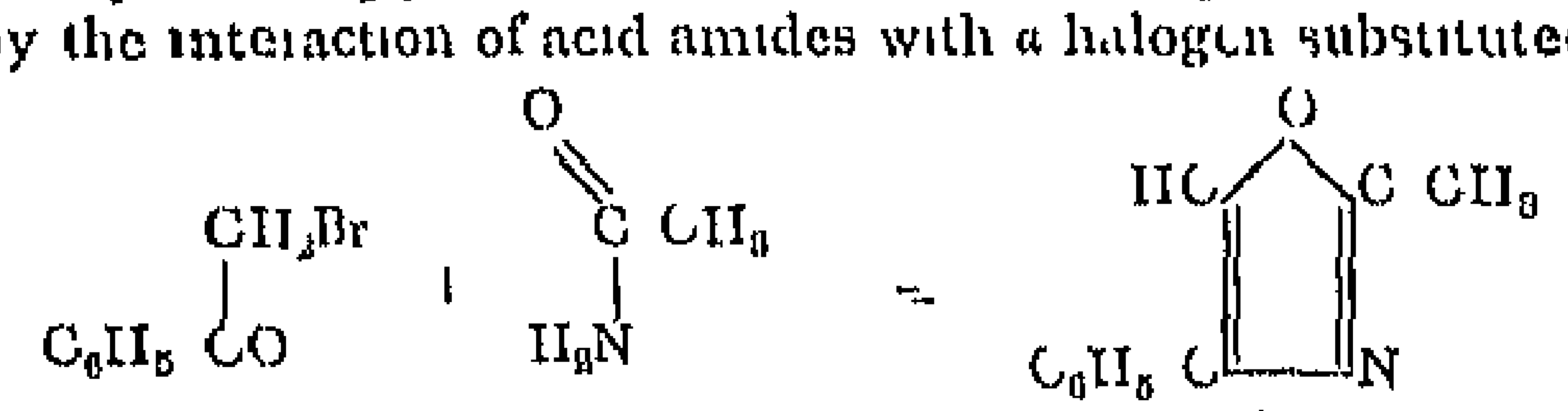


In an analogous manner α alkyl isoxazoles, in which the γ position is unsubstituted, are attacked comparatively rapidly by alkalis and instantaneously by sodium ethoxide, forming salts of the isomeric cyano ketones, *e g*,



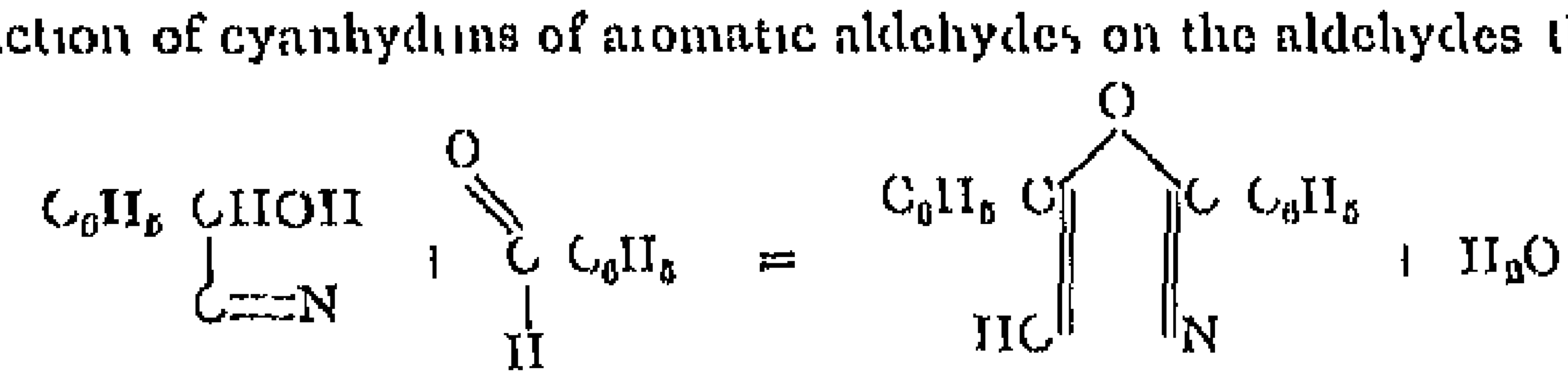
On the other hand, α γ dialkyl isoxazoles are extremely stable towards alkalis

Oxazoles correspond to glyoxalines or iminazoles A general method for their preparation is by the interaction of acid amides with α halogen substituted ketones,



Bromo acetophenone Acetamide μ Methyl β phenyl oxazole

or by the action of cyanhydrins of aromatic aldehydes on the aldehydes themselves [2]

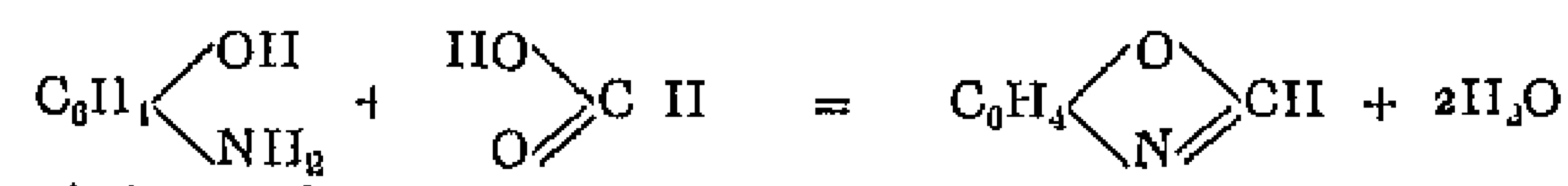


Benzaldehyde cyanhydrin α, μ Diphenyl oxazole

[1] J Schmidt and Wiedmann, *Ber*, 1909, 42, 1869 [2] F Fischer, *Ber*, 1896, 29, 207

The oxazoles are weak bases, and in many cases the ring is comparatively easily ruptured. Oxazole itself, the simplest member of the group, has not yet been prepared.

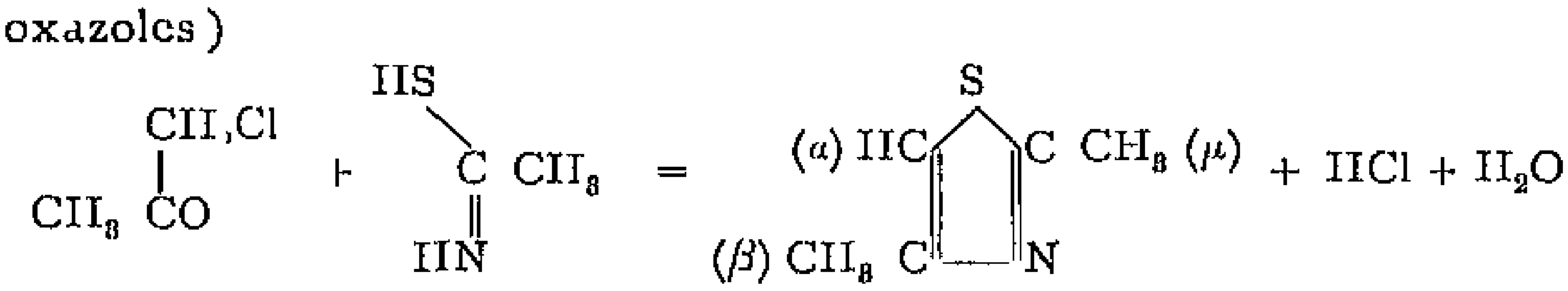
The **benzoxazoles** may be compared to the benziminazoles. Just as the latter are obtained from *o*-diamino benzenes, the former result from *o*-aminophenols by condensation with carboxylic acids:



o-Aminophenol. Benzoxazole (m.p. 30.5, b.p. 182.5.)

Benzoxazoles possess a weak basic character, and on being heated with hydrochloric acid decompose into their components—aminophenols and carboxylic acids.

Thiazoles are formed by the interaction of thioamides and *a*-chloroketones or *α*-chloro-aldehydes.[1] (Compare method given above for oxazoles.)



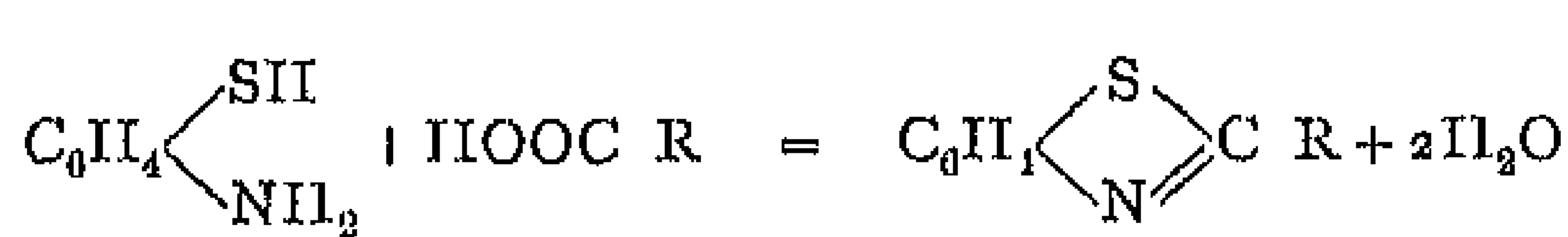
Chloroacetone. Thioacetamide. β, μ-Dimethyl thiazole.

If thiourea is used in this reaction μ-amino-thiazoles are formed, which on treatment with nitrous acid and alcohol exchange the amino-group for hydrogen, with the production of thiazoles.

Thiazole stands in the same relationship to pyridine as thiophene does to benzene. As has already been shown on pp. 587 and 588, the last two compounds possess many properties in common, and a similar resemblance exists between thiazole and pyridine. Thiazole itself is prepared by the above method from μ-amino-thiazole, and forms a mobile, volatile liquid, boiling at 117°, with a smell like pyridine. It is less basic than the latter.

A large number of derivatives of thiazole are known, which cannot be described here.

Benzo-thiazoles resemble the quinoline bases, and correspond in their composition to the benzoxazoles and benziminazoles. They are produced by the action of acids on *o*-amino-thiophenols:

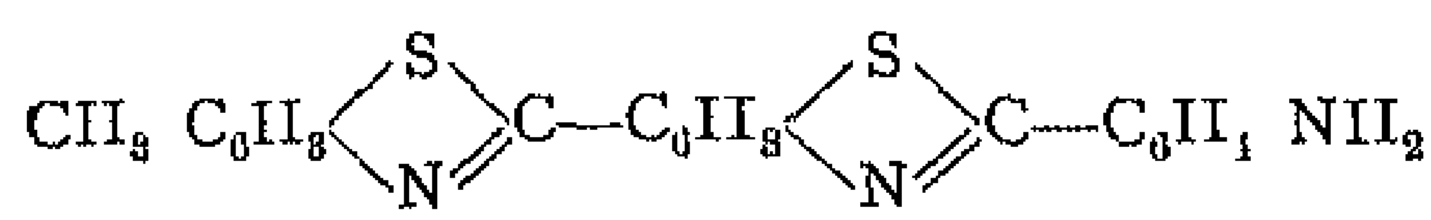


Certain derivatives of this group are of value as substantive cotton dyes.

Thus when *p*-toluidine and sulphur are heated together for a

[1] Hantzsch, *Ann.*, 260, 257.

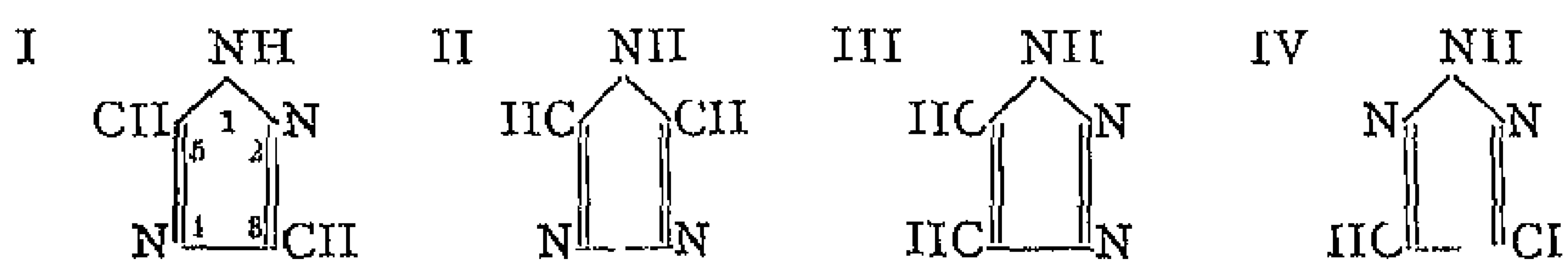
considerable time at 200°, a product known as "**primuline base**" is obtained, containing the following thiazole derivative



This is readily sulphonated to give **primuline**, which dyes cotton a yellow colour without the aid of mordants

IV —TRIAZOLES OR PYRRODIAZOLES

If two of the CH-groups in pyrrole are replaced by two N atoms, four different ring systems may be derived, as represented by the following formulæ —



1 2 4- 1 3 4- 1 2 3- 1 2 5-Triazole

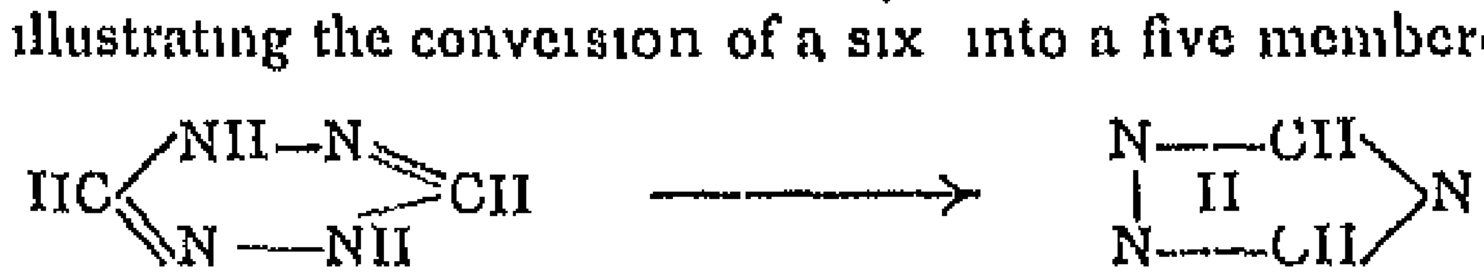
In this series we meet with tautomeric phenomena recalling those described under pyrazole (see pp. 614 *et seq*) Whereas all four compounds are known in the form of their N-alkyl and N-aryl derivatives, the parent substance I appears to be identical with II., and similarly III with IV For this reason it is convenient to make use of the following formulæ

sym Triazole *v*-Triazole, osotriazole

in which the position of the mobile hydrogen atom is not specified

Sym **Triazole** is obtained by various reactions, *e g* by the condensation of formyl hydrazide with formamide

and also by the action of nitrous acid on hydro tetrazine[1] This last reaction is of interest as illustrating the conversion of a six into a five membered ring



[1] Hantzsch and Silberrad, *Ber*, 1900, **33**, 58

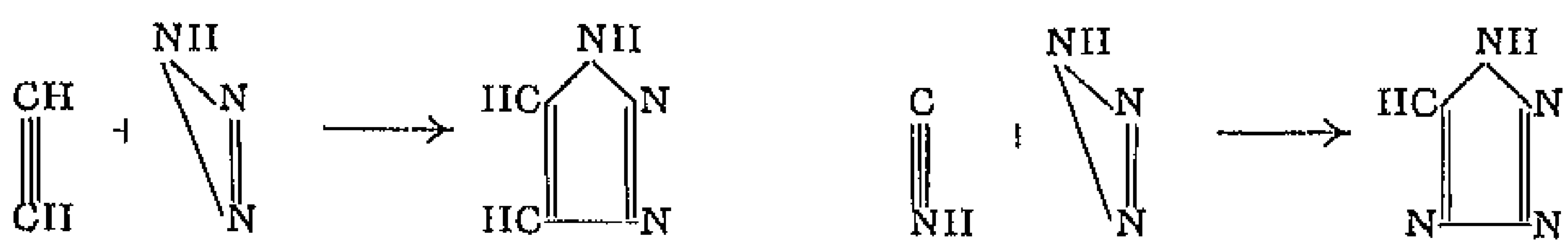
Both these methods are of general application, and symmetrical or true triazoles can therefore be prepared

1 From dihydro tetrazines [1]

2 By the action of acid hydrazides on amides Instead of starting from the hydrazide itself, the hydrazine hydrochloride may be heated with two molecular proportions of the amide In this case ammonia is first liberated with the formation of a hydrazide, which then acts upon the second molecule of amide

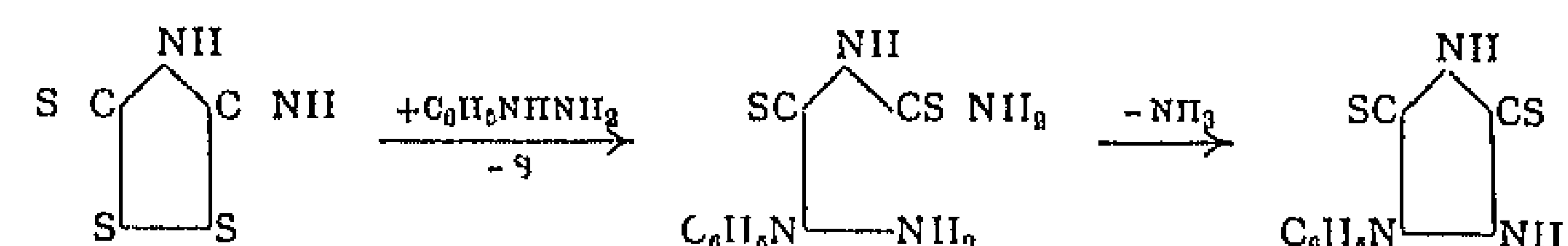
3 By warming the acid derivatives known as hydrazidines (Pinner [2])

1 2 3 Triazole is formed by the union of acetylene and hydrazoic acid The latter also unites with hydrogen cyanide, forming tetrazole [3]



Phenylazide, $C_6H_5N_3$, and sodium ethoxide in boiling alcoholic solution give 1 phenyl 1 2 3 triazole (m p 56) as the main product of reaction [4] The use of diazobenzene imide and higher alkoxides leads in general to the formation of 4 alkyl 1 phenyl-1 2 3 triazoles

Sulphur derivatives of triazole are produced by the action of phenyl hydrazine on persulphocyanic acid [5]

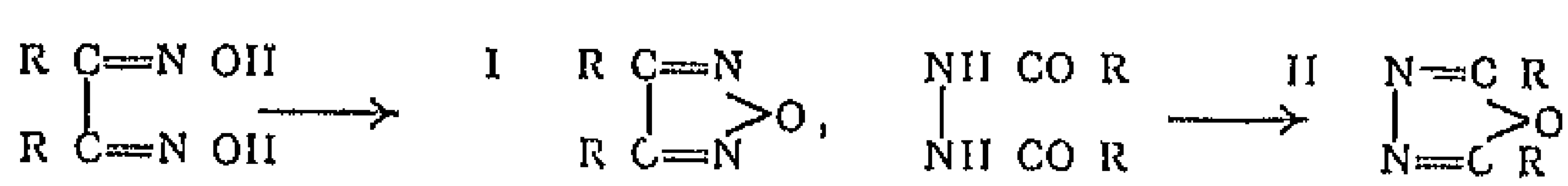


Persulphocyanic acid — Intermediate product — Phenyl dithio triazolidone

Triazole sublimes in needles, m p 120° to 121° and b p 260° (100° under 0 1 mm pressure) It is a weak base ($K=2\ 2 \times 10^{-12}$) but yields metallic salts, *e g* $(C_2H_2N_3)_2Cu$

In general, the triazoles closely resemble the pyrazoles in behaviour, but are even more stable towards oxidising agents They are all very weak bases, although the introduction of two methyl or ethyl groups somewhat increases the basic strength As in the case of the pyrazoles, a number of interesting tautomeric phenomena have been discovered among the 1 2 3 triazoles [6]

Other ring compounds of similar type are the **furazanes** (I), resulting from the oximes of α diketones by removal of water, and the **oxydiazoles** (II), obtained from symmetrical diacyl hydrazines

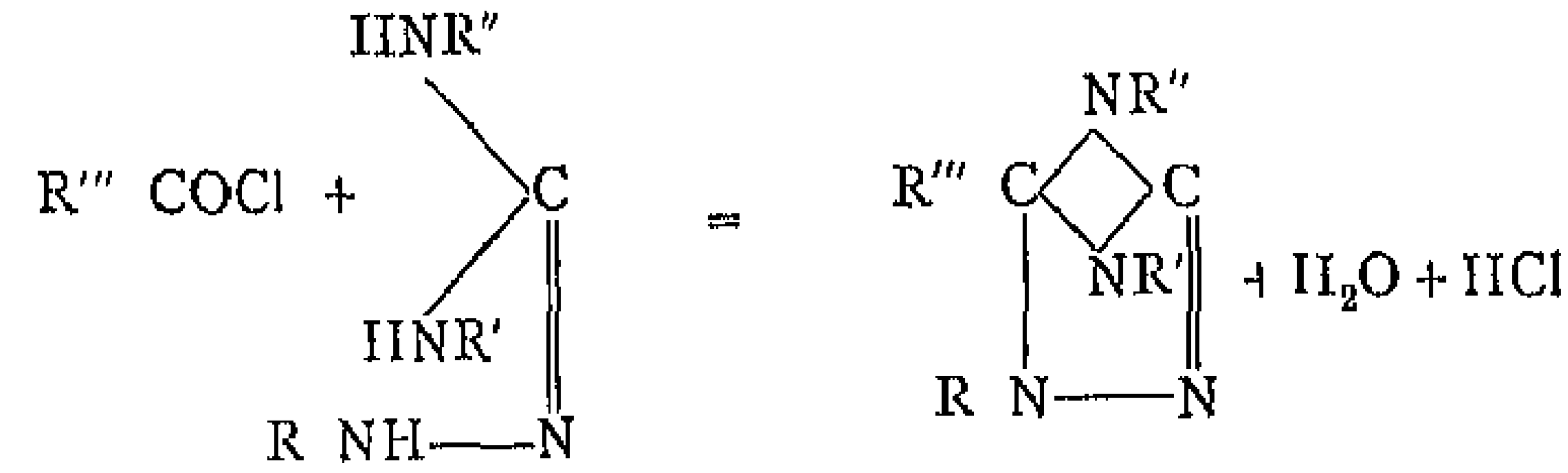


[1] Busch and Heinrichs, *Ber* , 1900, 33, 455 [2] Pinner, *Ann* , 297, 221 , 1898, 298, 1
[3] O Dimroth and co workers, *Ber* , 1910, 43, 2219, 2899 [4] A Bertho, *Ber* , 1925, 58, 859
[5] Fromm and co workers, *Ann* , 1906, 348, 171 , *Ber* , 1923, 56, 1370, [6] Dimroth, *Ann* , 1909, 364, 183

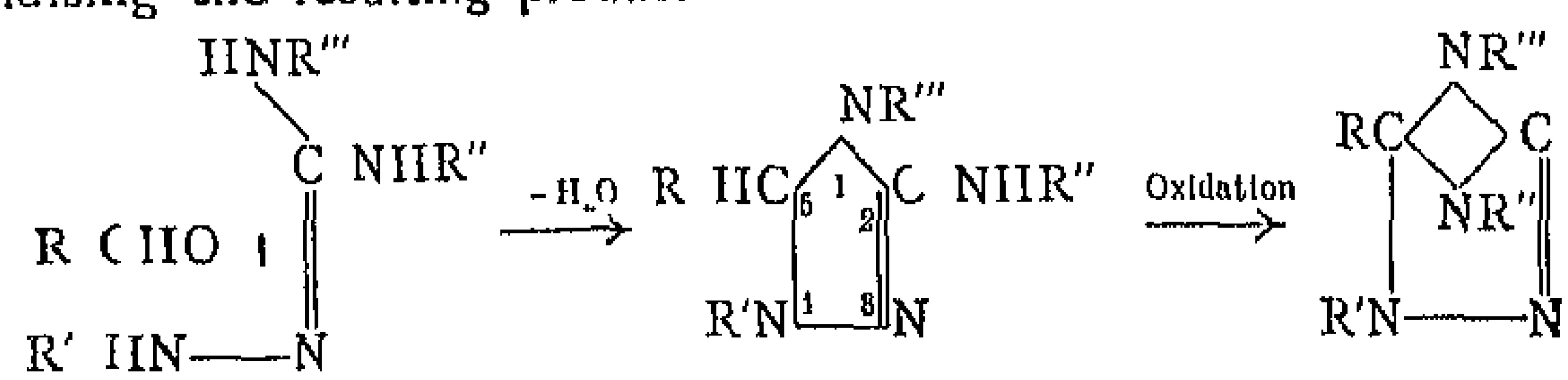
Endimino-triazoles

Peculiar triazole bases containing a "nitrogen bridge," and known as endimino-triazoles, have been prepared by Busch [1] They are produced

1 From acid chlorides and triarylamino-guanidines,



2 By condensing aldehydes with triarylamino-guanidines and oxidising the resulting products



1 4 5-Trialkyl-3 alkylamino dihydro triazole

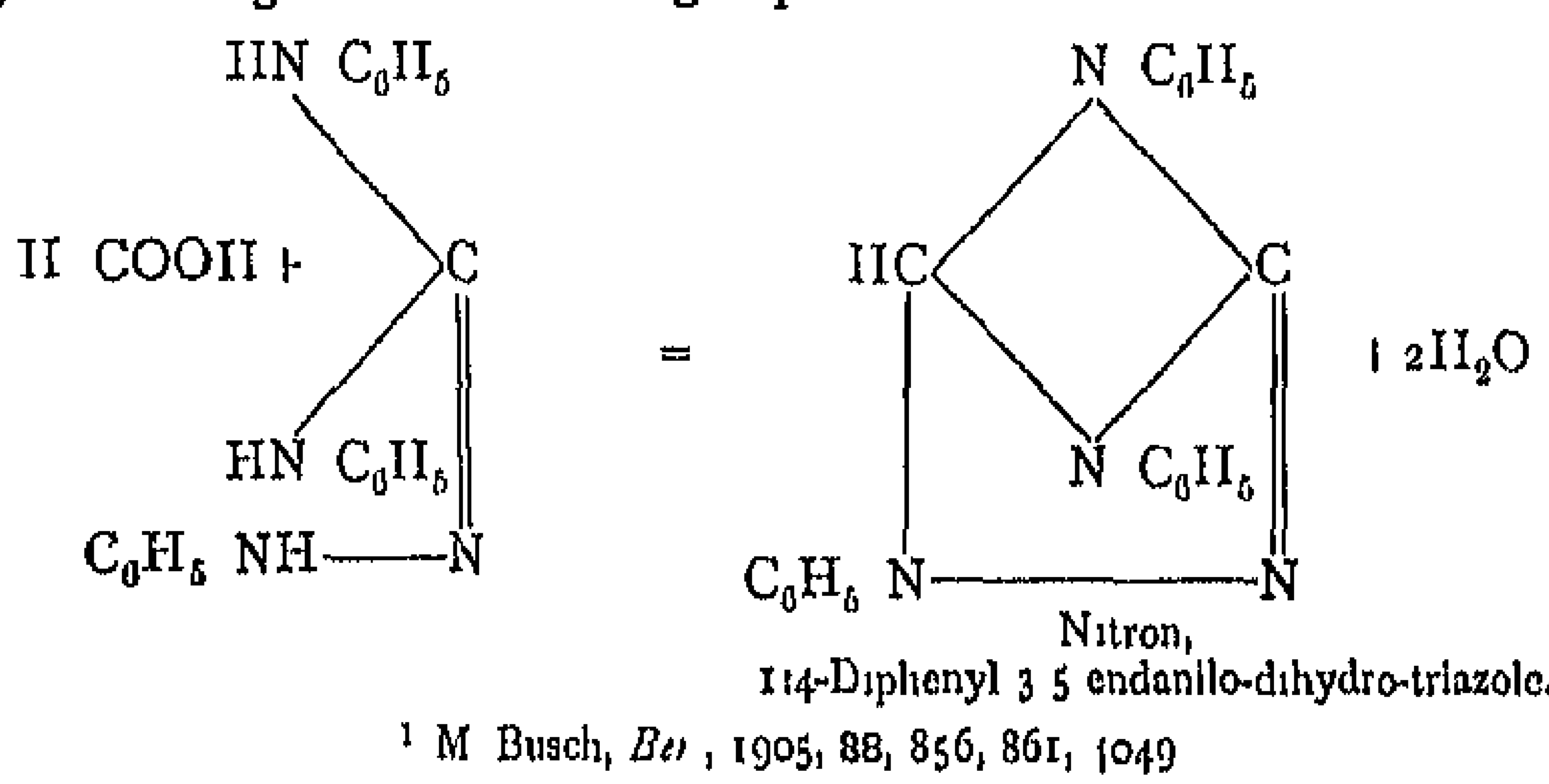
An endimino triazole

Most of the endimino-triazoles are yellow compounds, which possess strong basic character and crystallise well Although very stable towards acids, they are readily decomposed into their original components by alkalis

Endimino triazoles are also of practical interest in so far as their nitrates are much more sparingly soluble than any other nitrates yet examined, so that these bases may be employed as a reagent for the nitrate ion

The nitrate of 1 **4-diphenyl-endanilo-dihydro-triazole** is the least soluble of these compounds and may be used successfully for the *qualitative* and also the *quantitative estimation of nitric acid* For this reason the base has been termed **nitron**

Nitron is prepared from triphenyl-aminoguanidine and formic acid, according to the following equation



Nitron,
1:4-Diphenyl 3 5 endanilo-dihydro-triazole.

[1] M Busch, *Ber*, 1905, 38, 856, 861, 1049

It crystallises in yellow leaflets or plates which melt with decomposition at 189°

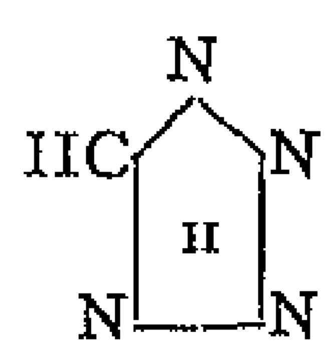
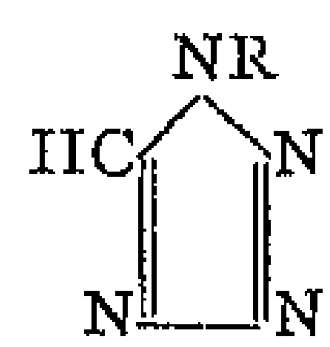
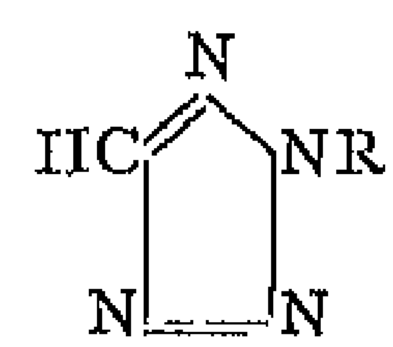
As a reagent, a 10 per cent solution of nitron in 5 per cent acetic acid is used About 5 to 6 c c of the liquid under examination are acidified with one drop of dilute sulphuric acid, and five to six drops of the nitron solution added In the presence of nitric acid a voluminous white precipitate immediately separates, and by this means nitric acid may be detected even at a dilution of 1 in 60,000

Nitron may also be employed for the detection and estimation of nitrates in the presence of nitrites[1]

V —TETRAZOLES

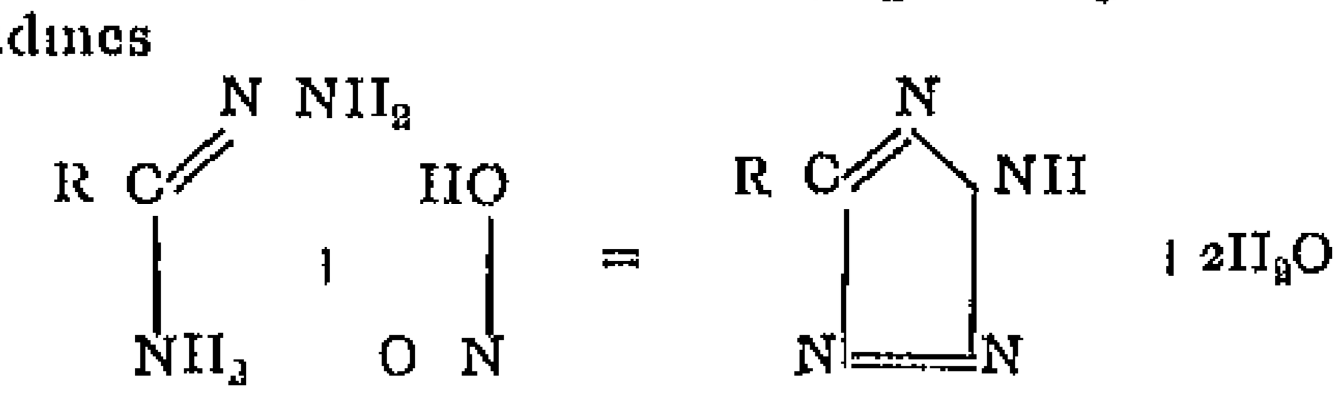
Tetrazoles contain a ring system built up from one carbon and four nitrogen atoms

Once again tautomeric phenomena are observed, similar to those described in the case of pyrazole and triazole, the one parent compound (I) giving rise to two series of derivatives (I*a* and I*b*)

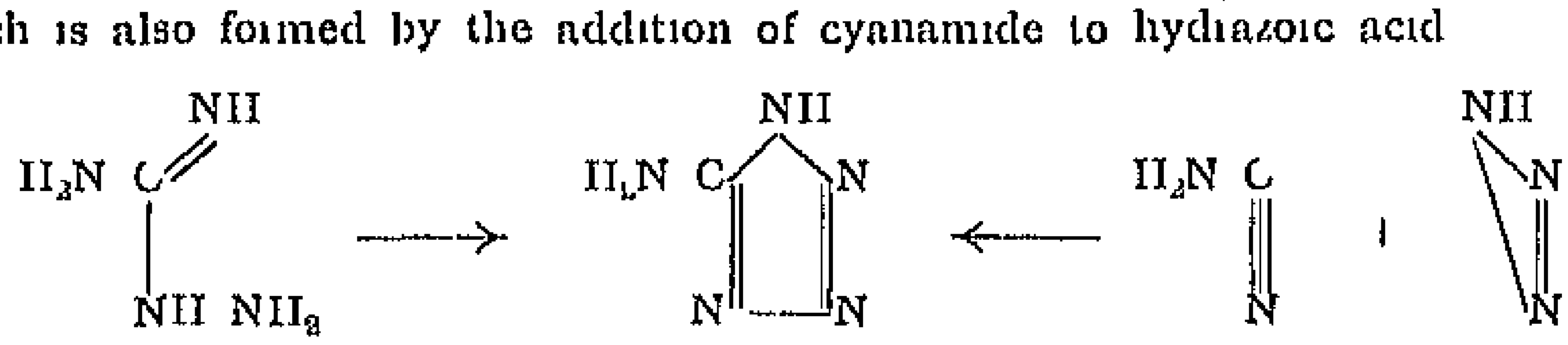
I  I*a*  I*b* 

Owing to the mobility of the double bonds, the hydrogen compounds corresponding to the types I*a* and I*b* are in a state of dynamic equilibrium with one another, and isomerism can only be detected if intramolecular change is retarded by substituting the imino-hydrogen atoms[2]

Tetrazoles are formed by various reactions, *e g* with great readiness from nitrous acid and hydrazidines



An arrangement of atoms similar to that in the hydrazidines is present in amino guanidine The latter on treatment with nitrous acid yields amino tetrazole, which is also formed by the addition of cyanamide to hydrazoic acid



[1] M Busch, *Ber* , 1905, 38, 863 For the determination of nitric acid in water, see Busch, *J C S*, A, 1905, ii , 418 [2] Wedekind, *Ber* , 1896, 29, 1846 M Freund, *Ber* , 1901, 34, 3110

Tetrazole may be obtained from amino tetrazole by way of the diazo-compound in the same manner as benzene is obtained from aniline

For the formation of tetrazole from hydrazoic acid, see p 629, and for the synthesis of tetrazoles from diazobenzene imide, see O Dimroth and Merzbacher, *Ber*, 1907, 40, 2402

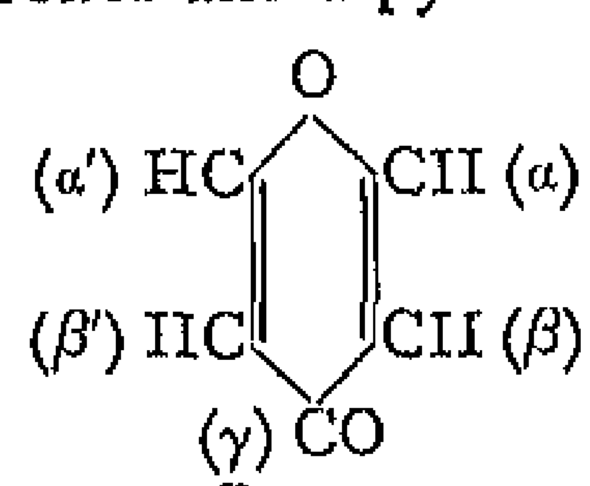
The tetrazole ring is very similar in nature to the benzene ring Those tetrazoles containing a free imino-group are strong monobasic acids The silver and copper salts of tetrazoles explode with violence on heating

Tetrazole forms colourless crystals of melting-point 156°, and its aqueous solution is acid in reaction It possesses no basic properties and gives no nitroso derivative

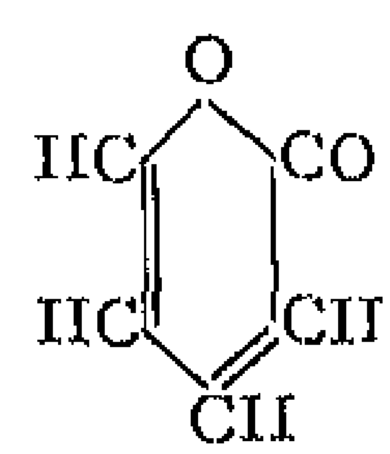
IV

Pyrones

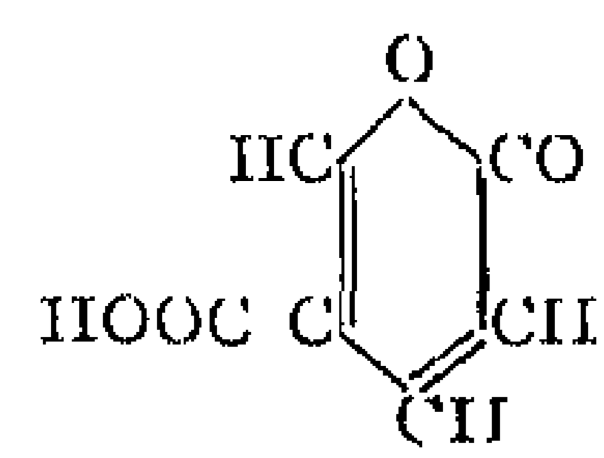
The pyrone ring contains five carbon atoms and one oxygen atom, and according to their arrangement a distinction is drawn between γ-pyrones and α pyrones,



γ-Pyrone
m p 32°, b p 315°



α-Pyrone
b p 206 209°



Coumalic acid

Benzo-derivatives of α-pyrone have already been described on p 449, under *coumarins*, the γ lactones of unsaturated aliphatic-aromatic *o* hydroxy acids A simple derivative of α-pyrone is *coumalic acid* (coumalinic acid), which can be prepared from malic acid (see p 278) In the following pages will be found a description of the *γ-pyrones, generally known as pyrones*

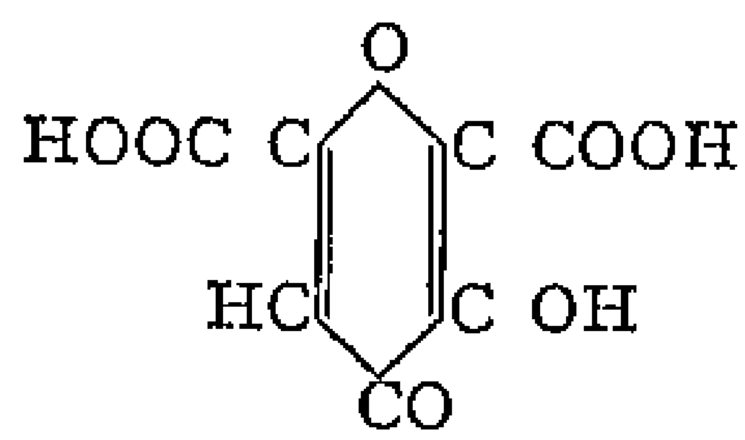
γ-PYRONES

γ-Pyrone is the parent compound of a series of substances found in nature, *e g* brazilin,[1] the colouring matter of red-wood, and in recent years the pyrones have also attracted interest in connection with investigations on the basic properties of oxygen

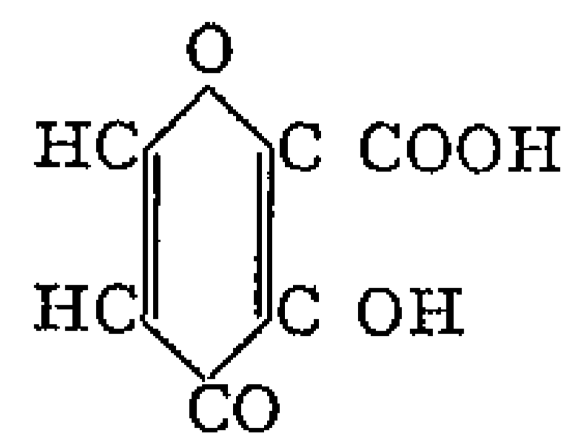
A naturally occurring derivative of γ-pyrone is the **meconic acid** present in opium On being heated, this acid parts with carbon

[1] See Crabtree and R Robinson, *J C S*, 1918, 113, 872 W H Perkin, J N Rây, and R Robinson, *J C S*, 1927, 2094 P Pfeiffer and co workers, *Ber*, 1924, 57, 208, 1927, 60, 2142, 1928, 61, 839

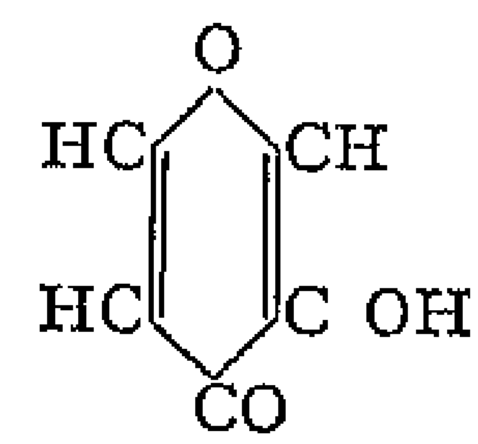
dioxide to form *comenic acid* and finally *pyromeconic acid* (also known as pyrocomenic acid)



Meconic acid,
β hydroxy pyrone
α α'-dicarboxylic acid

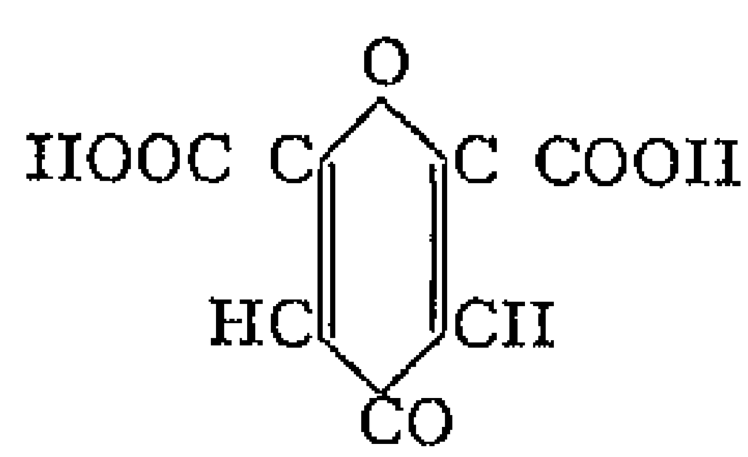


Comenic acid,
β hydroxy pyrone
α-carboxylic acid

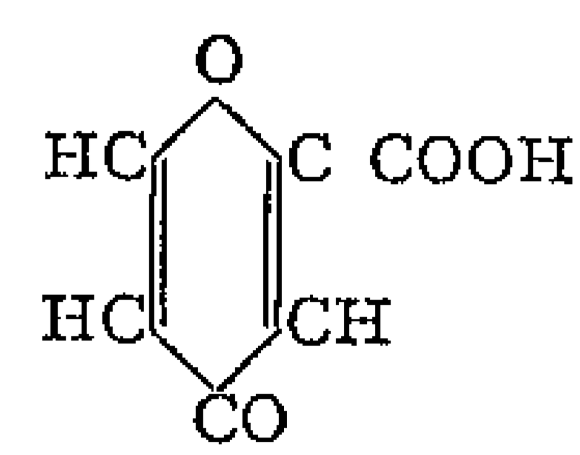


Pyromeconic acid,
β hydroxy γ pyrone
(m p 121°)

Another compound of the same type is **chelidonic acid**, found in the celandine and white hellebore. On being heated, this yields *comanic acid* and then pyrone.

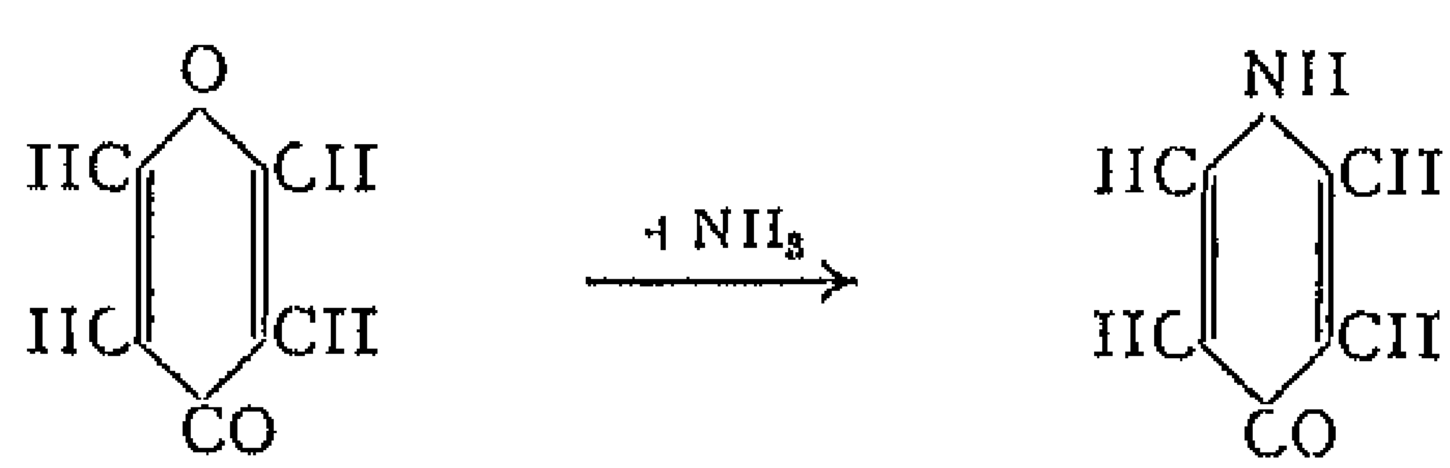


Chelidonic acid,
pyrone α α'-dicarboxylic acid
(m p 262°)



Comanic acid,
pyrone-α carboxylic acid
(m p 250° with decomp)

The close relationship existing between the pyrones and pyridones is at once visible on comparing the formulæ of these two series of compounds, and is also confirmed by experiment, since the pyrones on treatment with ammonia are readily converted into the corresponding pyridones. In this change the ring oxygen atom is replaced by the NH-group, and it has been suggested that various alkaloids derived from pyridine are synthesised in this manner in the tissues of plants

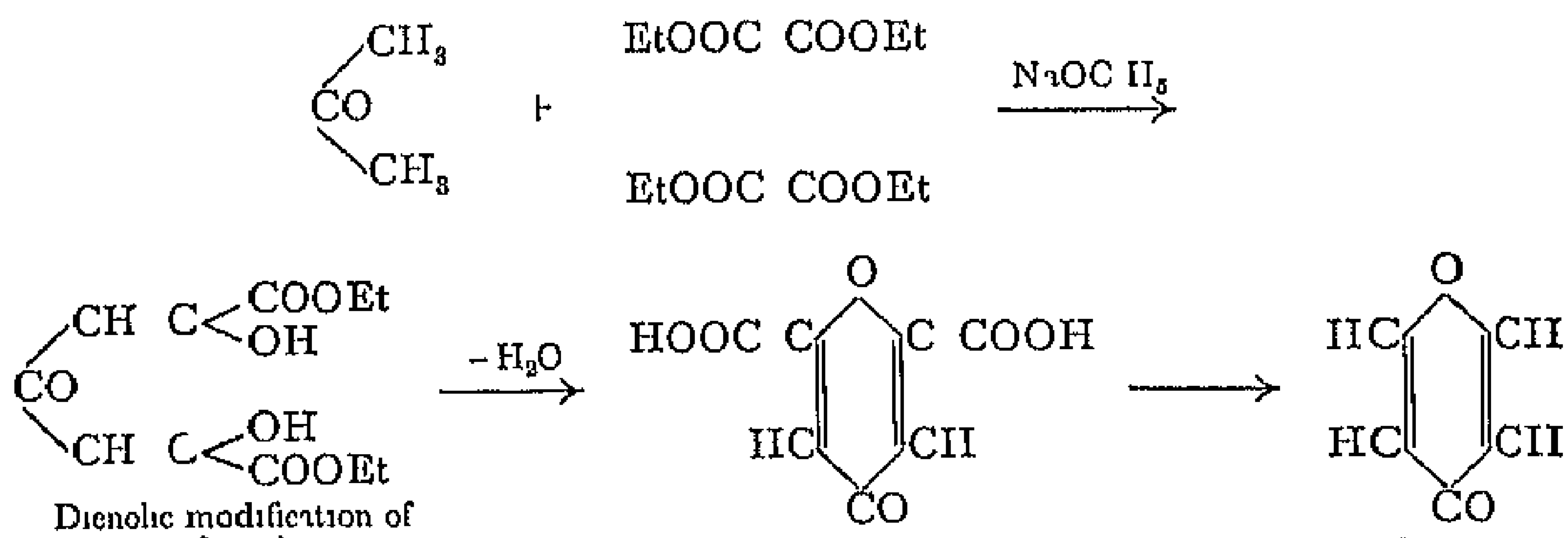


γ Pyrone γ Pyridone

The *synthesis of chelidonic acid and pyrone* may be effected from acetone-dioxalic ester[1]. The latter is obtained by condensing acetone with two molecules of oxalic ester, and very readily loses water—even on boiling in alcoholic solution—to form chelidonic ester. When acetone-dioxalic ester is heated with hydrochloric acid, loss of water

[1] Willstätter and Pummerer, *Ber*, 1904, 37, 3734, 3744; 1905, 38, 1465. For the conversion of dibenzal-acetone into *αα' diphenyl pyrone*, see D Vorländer and Meyer, *Ber*, 1912, 45, 3355

and hydrolysis take place simultaneously, with direct production of chelidonic acid. Pyrone may be obtained from chelidonic acid by dry distillation, preferably with the addition of copper powder.

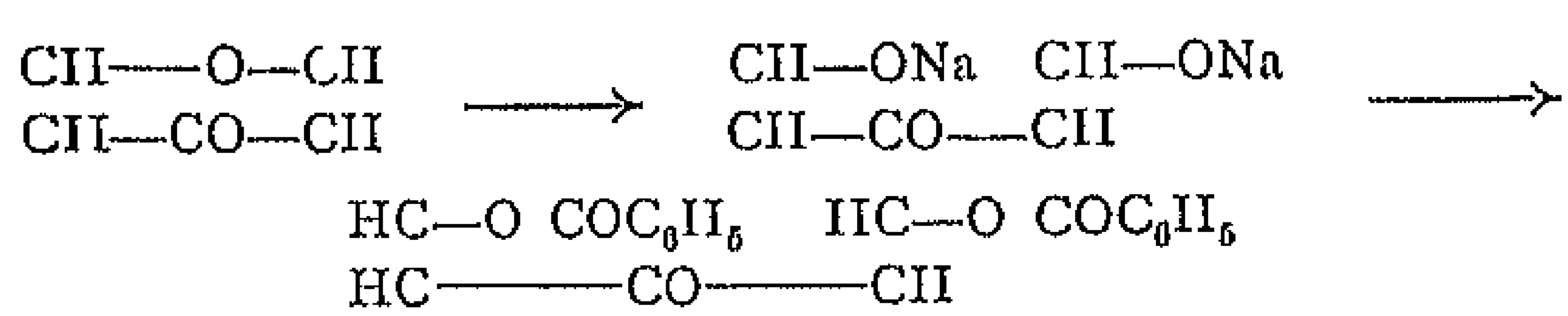


Dienolic modification of acetone-dioxalic ester — Chelidonic acid — Pyrone

Chelidonic acid and pyrone are readily disrupted to give open chain compounds. On being boiled with alkali, the former decomposes smoothly into 1 mol. acetone and 2 mols. oxalic acid,

$$C_7H_4O_6 + 3H_2O = 2HO_2C \cdot CO_2H + CH_3 \cdot CO \cdot CH_3$$

Pyrone is easily converted into derivatives of bis-*hydroxymethylene-acetone*.[1] Even a short treatment with alkali in the cold is sufficient to bring about this change. The reaction may be conveniently followed by adding benzoyl chloride to the alkaline liquid, when the bis-hydroxymethylene-acetone separates out in the form of its dibenzoate.



Dibenzoate of *bis* hydroxymethylene acetone

Owing to its insolubility, this dibenzoyl compound provides a useful means of testing for pyrone itself in dilute aqueous solution.

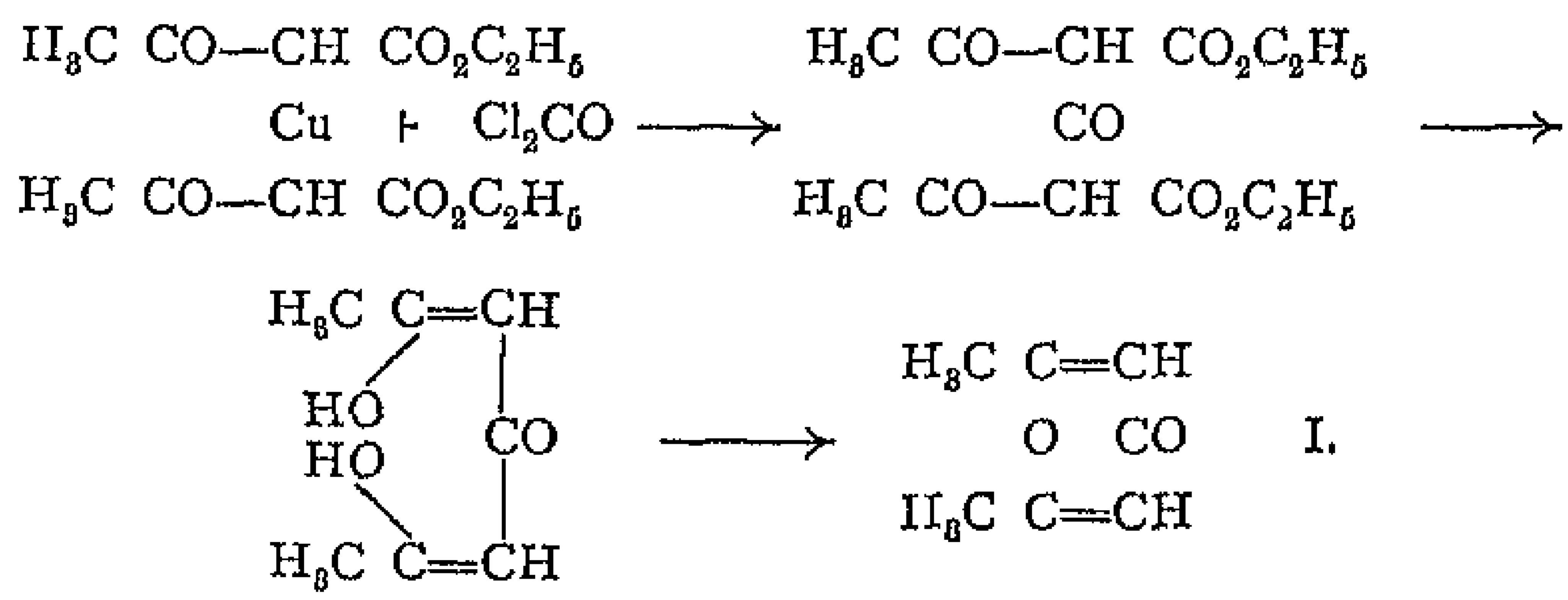
A similar opening of the pyrone ring is produced by the action of aniline acetate, when the dianilide of bis-hydroxymethylene-acetone is formed.[2]

Salt Formation with Dimethyl-pyrone and Pyrone, and the Tetravalency of Oxygen

Dimethyl-pyrone (I.), m.p. 132° and b.p. 248°, has been used by Collie and Tickle[3] as the basis of an investigation into the tetravalency of oxygen. It may be prepared by condensing the copper salt of

[1] Willstätter and Pummerer, *Ber.*, 1904, **37**, 3734, 3744; **38**, 1465. [2] W. Borsche and Bonacker, *Ber.*, 1921, **54**, 2678. [3] Collie and Tickle, *J. C. S.*, 1904, **85**, 971.

acetoacetic ester with phosgene, and boiling the product so obtained with sulphuric or hydrochloric acid [1]



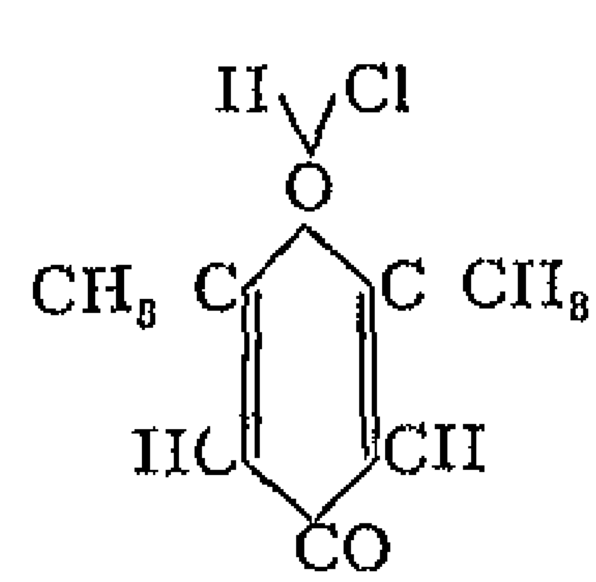
I.

In the research quoted above, Collie and Tickle showed that dimethyl-pyrone forms addition products with a number of acids, such as $C_7H_8O_2, HCl$ with hydrochloric acid, $(C_7H_8O_2)_2, H_2PtCl_6$ with hydrochloroplatinic acid, and $(C_7H_8O_2)_2, C_4H_6O_6$ with tartaric acid It will be seen that these all result from the direct addition of acid, without loss of water

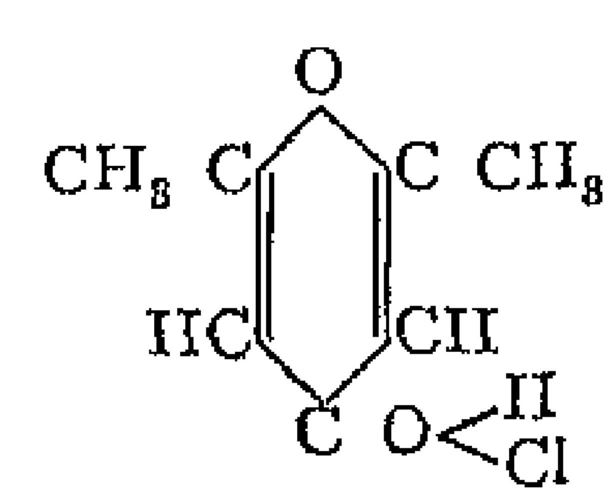
The stability and behaviour of these compounds can be explained on the assumption of a tetravalent oxygen atom with basic properties It therefore appears that oxygen can take the place of sulphur, phosphorus and nitrogen in bases, to form derivatives of a hypothetical base, which is known as *oxonium hydroxide*, $H_3O\ OH$, by analogy with the hypothetical bases $NH_4\ OH$, $PH_4\ OH$, $H_3S\ OH$, $H_2I\ OH$ Salts of this oxygen base are known as **oxonium salts** [2]

In this connection it will be seen that dimethyl-pyrone contains two oxygen atoms, leading to the possibility of either of the formulæ I*a* or I*b*

I*a*



I*b*



[1] F Feist, *Ann*, 1890, **257**, 253 Willstätter and Pummerer, *Ber*, 1905, **38**, 1465 [2] By mixing dimethyl-pyrone with a saturated solution of cupric chloride, A Werner (*Ann*, 1902, **322**, 312) obtained the compound $C_7H_8O_2, CuCl_2$ This lends support to his hypothesis that the formation of oxonium salts depends, not upon the tetravalency of oxygen, but on the presence of an unsaturated subsidiary valency in this element, the saturation of which may take place in a variety of ways In formulæ based on this conception the subsidiary valency is indicated by a dotted line, addition products obtained from acids and an oxygen compound being represented by the formula $\begin{matrix}R\\R\end{matrix}\!>O$ XII A résumé of recent work on oxonium compounds will be found in papers by J Kendall, *J Am C S*, 1917, **39** 2303, and Knox and Richards, *J C S*, 1919, **115**, 508

for dimethyl-pyrone salts So far it has not been found possible to decide with certainty between these two types, although the structure I*b* seems the more probable Experience shows that the carbonyl oxygen possesses more free affinity than the oxygen of ethers

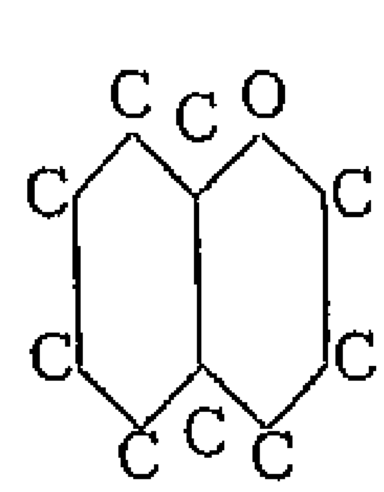
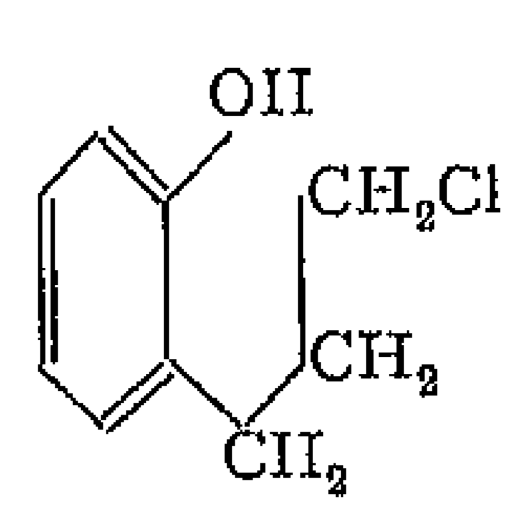
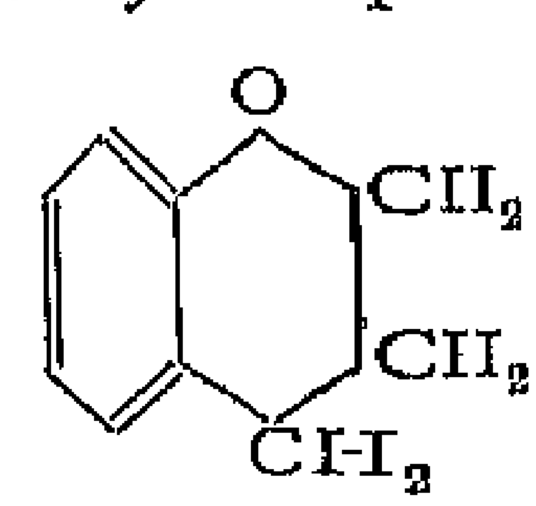
An examination of the electrical conductivity of dimethyl-pyrone salts in aqueous solution indicates that they are almost completely hydrolysed Dimethyl pyrone also unites with methyl sulphate to give an addition product, which on treatment with potassium iodide yields dimethyl-pyrone methiodide, of the composition CH_3I + dimethyl pyrone

Salts are also formed by the parent compound pyrone (*e.g* hydrochloride, picrate and oxalate), but in this case there is a strong tendency towards the formation of more complex salts[1] Pyrone combines, in addition, with inorganic salts such as calcium chloride, mercuric chloride and silver nitrate In this respect it resembles the amino acids, in which Strecker assumes that the carbonyl group binds the metallic radical, and the amino group the acidic radical of the salts This would point to the tetravalent oxygen of pyrone possessing both basic and acidic character, and is in agreement with Walden's assumption—based on conductivity experiments—that dimethyl-pyrone is an *amphoteric electrolyte*[2]

The discovery of the salts of dimethyl-pyrone, and their formulation as oxonium salts, has stimulated research into the question as to whether salt formation is a property of oxygen compounds in general Experimental results obtained by Baeyer and Villiger[3] indicate that this is the case, and in recent years evidence has been supplied by other investigators confirming the existence of a great variety of addition compounds, which are regarded as salts of tetravalent oxygen,[4] (see pp 128, 151, 556)

BENZO- AND DIBENZO-γ-PYRONE

The cyclic oxide chromane (formula III below) may be regarded as the parent compound of a number of derivatives such as the chromones and coumarins, containing the atomic framework (I) **Chromane** has been prepared from the base tetrahydro-quinoline[5]

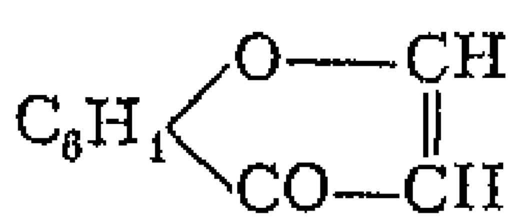
I.  II  III 

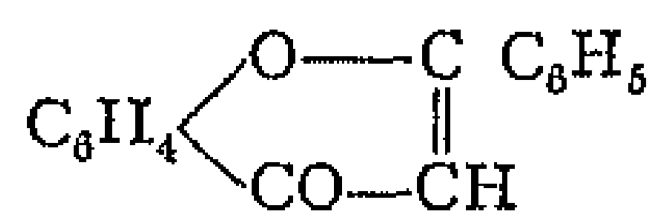
[1] A Werner, *Ann*, 1902 322, 296 Willstätter and Pummerer, *Ber*, 1904, 37, 3740
[2] *Ber*, 1901, 34, 4185, 1902, 35, 1764 [3] Baeyer and Villiger, *Ber*, 1901, 34, 2679
[4] See Knox and Richards, *J C S*, 1919, 115, 508, and J Kendall, *J Am C S*, 1917, 39, 2303
[5] Braun and Steindorff, *Ber*, 1905, 38, 850

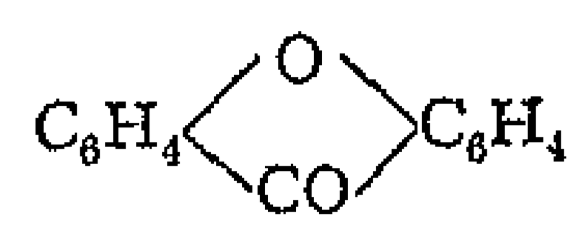
(see p 658) The nitrogen ring of the latter may be opened to give o-γ-chloropropyl-aniline, which by means of the diazo reaction can be converted into o-γ-chloropropyl-phenol (II) In alkaline solution this is quantitatively transformed into chromane

Chromane is a strongly refractive liquid, which smells like peppermint and boils at 214° to 215° (749 mm press) It dissolves, in concentrated sulphuric acid, giving a pink solution

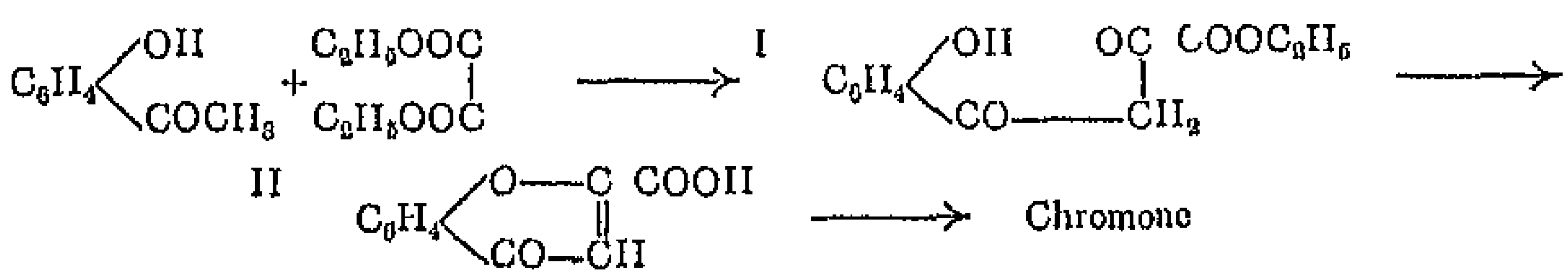
From benzo-pyrone, or chromone, and dibenzo-pyrone, or xanthone are derived a number of naturally occurring yellow dyes, the colour of which is due to the chromophore CO


Chromone,
benzo γ pyrone


Flavone,
β phenyl benzo γ pyrone

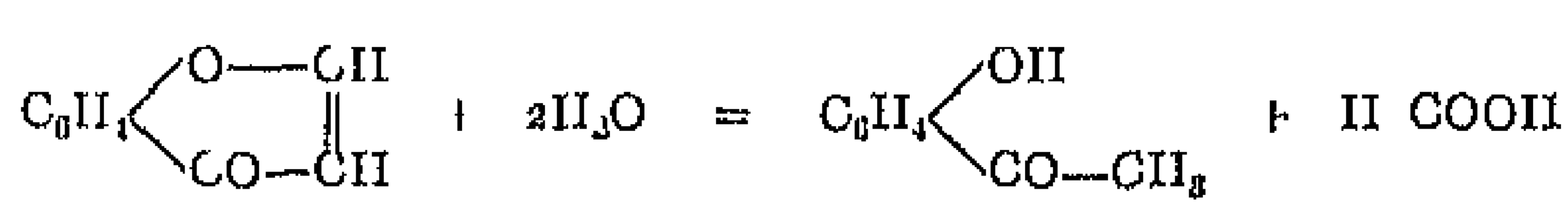

Xanthone,
dibenzo γ pyrone

Chromone can be synthesised from o hydroxy acetophenone and oxalic ester[1] In the presence of sodium these react with one another to form o hydroxy-benzoyl-pyroracemic ester (I), which, on boiling with alcoholic hydrochloric acid, loses a molecule of water and yields chromone carboxylic acid (II) The latter on distillation parts with carbon dioxide to form chromone This is a general method for the preparation of chromones.

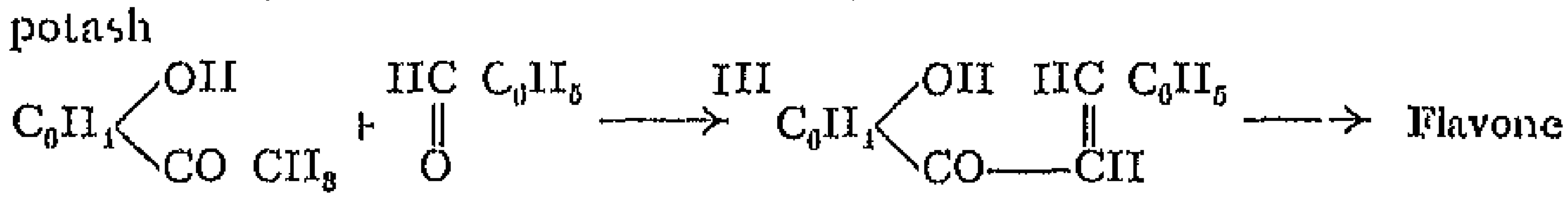


The reaction described on p 449, for the formation of coumarin derivatives from phenols and β ketonic esters, has been adapted to the preparation of chromones by modifying the conditions of condensation and using phosphorus pentoxide in place of sulphuric acid[2]

Chromone forms white needles, m p 59° When boiled with sodium ethoxide it decomposes into o hydroxy acetophenone and formic acid



Flavone, m p 99° to 100°, is prepared in various ways,[3] *e g*, o-hydroxy acetophenone condenses with benzaldehyde to give hydroxy-chalkone (III), which when acetylated and converted into the dibromide yields flavone on subsequent treatment with alcoholic potash



[1] Kostanecki and co workers, *Ber*, 1901, **34**, 2375, **35**, 859, 861, 2547, 2887 [2] Petschek and Simonis, *Ber*, 1913, **46**, 2014 [3] Kostanecki and co-workers, *Ber*, 1898, **31**, 1757, 1900, **33**, 330, 1904, **37**, 2634 Ghosh, *J C S*, 1916, **109**, 105

In this manner Kostanecki has synthesised a number of yellow dye-stuffs occurring in nature, all of which are mordant dyes and in general contain two hydroxyls in the *o* position to one another[1] Examples of this type are —

Chrysin, 1 3 *dihydroxy flavone*, $C_{15}H_{10}O_4$, a constituent of poplar buds

Luteolin, 1 3 3′ 4′ *tetrahydroxy flavone*, $C_{15}H_{10}O_6+2H_2O$, the dye of *dyer's weed*, Reseda luteola With aluminium mordant it dyes yellow, and is employed particularly for silk

Fisetin, 3 3′ 4′ trihydroxy flavonol, isomeric with luteolin, and a hydrolysis product of the glucoside **fustin** contained in young fustic

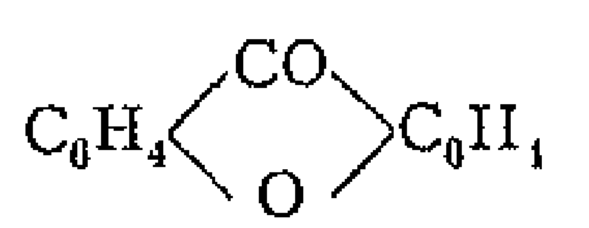
Quercetin, 1 3 3′ 4′ tetrahydroxy flavonol, $C_{15}H_{10}O_7$, a hydrolytic product of the glucoside **quercitin**, $C_{21}H_{22}O_{12}$, present in quercitron bark

Rhamnetin, methyl quercetin, a hydrolysis product of the glucoside **xanthorhamin** contained in Avignon berries and buckthorn berries

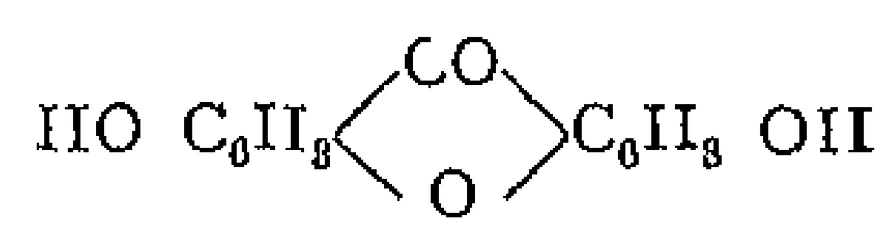
Morin, isomeric with quercetin, a constituent of the wood of *Morus tinctoria* ("fustic") Used in the form of an extract, particularly for dyeing wool

Finally we may mention **apigenin**,[2] or 1 3 4′-*trihydroxy-flavone*, obtained by the hydrolysis of the glucoside *apiin*, which occurs in parsley and to a smaller extent in celery

Xanthone can be prepared by the elimination of water from phenyl-salicylic acid The most interesting of its derivatives is euxanthone



Xanthone,
m p 174°, b p 350°

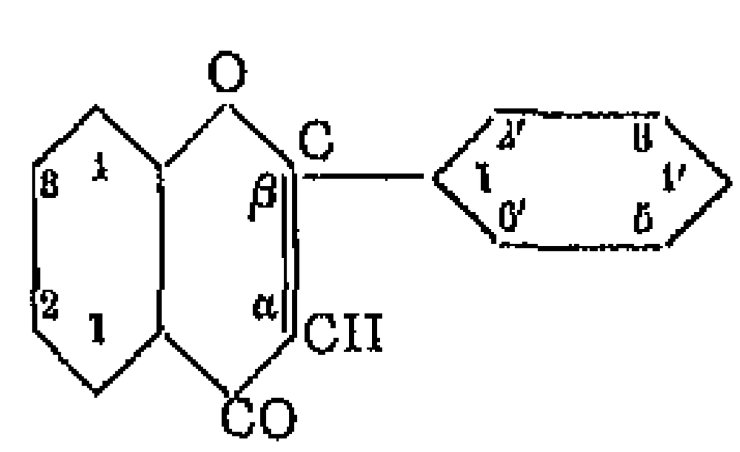


Euxanthone, dihydroxy xanthone,
b p 237°

Euxanthone[3] is prepared from the natural dye-stuff *purri* or Indian yellow, in which it occurs free and also in combination with glycuronic acid in the form of *euxanthic acid* The magnesium salt of euxanthic acid is the chief constituent of the Indian yellow of commerce, which is used as a painter's colour

Euxanthone can be synthesised from hydroquinone-carboxylic acid and resorcinol, the reaction is a general one, and by condensing hydroxy-acids with polyhydric phenols numerous xanthone derivatives can be prepared Up to the present, however, these are without practical value

[1] Position isomerides are described in accordance with the following notation proposed by Kostanecki—



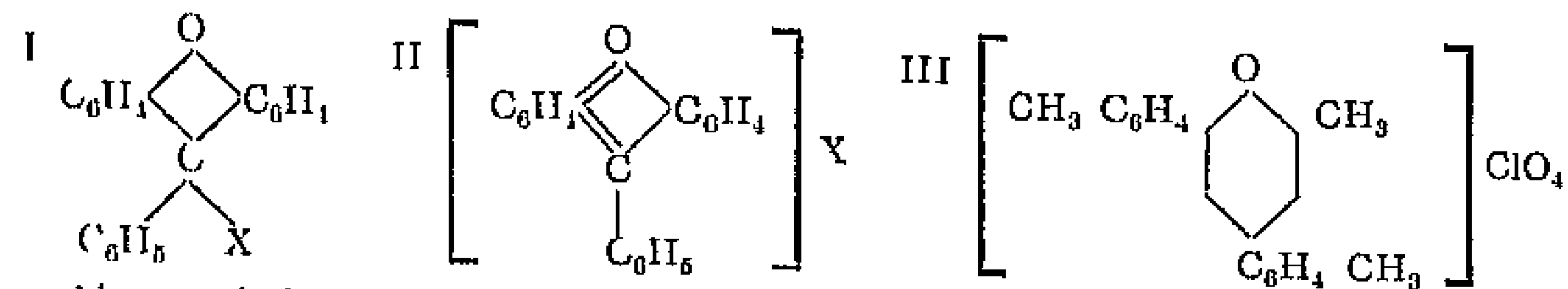
Flavone

Flavonol

[2] Kostanecki, *Ber*, 1900, 33, 1988 Vongerichten, *Ber*, 1900, 33, 2334 *Ann*, 1901, 318, 121

[3] For a synthesis, see Ullmann and Panchaud, *Ann*, 1906, 350, 108

Xanthylium and Pyrylium Salts.—Xanthylium salts stand in close relationship to the triarylmethylium salts already discussed on pp. 497 *et seq.* They only differ from the latter in containing an oxygen bridge between two of the benzene nuclei and hence the two classes of compounds have very similar properties. Gomberg and Cone showed that the xanthyl halogenides, although colourless, yield coloured products by further addition of salts or acids. The xanthylium compounds formed with oxygen acids, however, are without exception coloured. In these respects there is a complete resemblance to the triarylmethane derivatives. Kehrmann[1] found that in certain special cases even the simple halogenides of the xanthyl series may be coloured and then also possess the character of salts. By analogy with the triaryl compounds the colourless xanthyl derivatives are formulated as in I, the coloured salt-like compounds as in II.

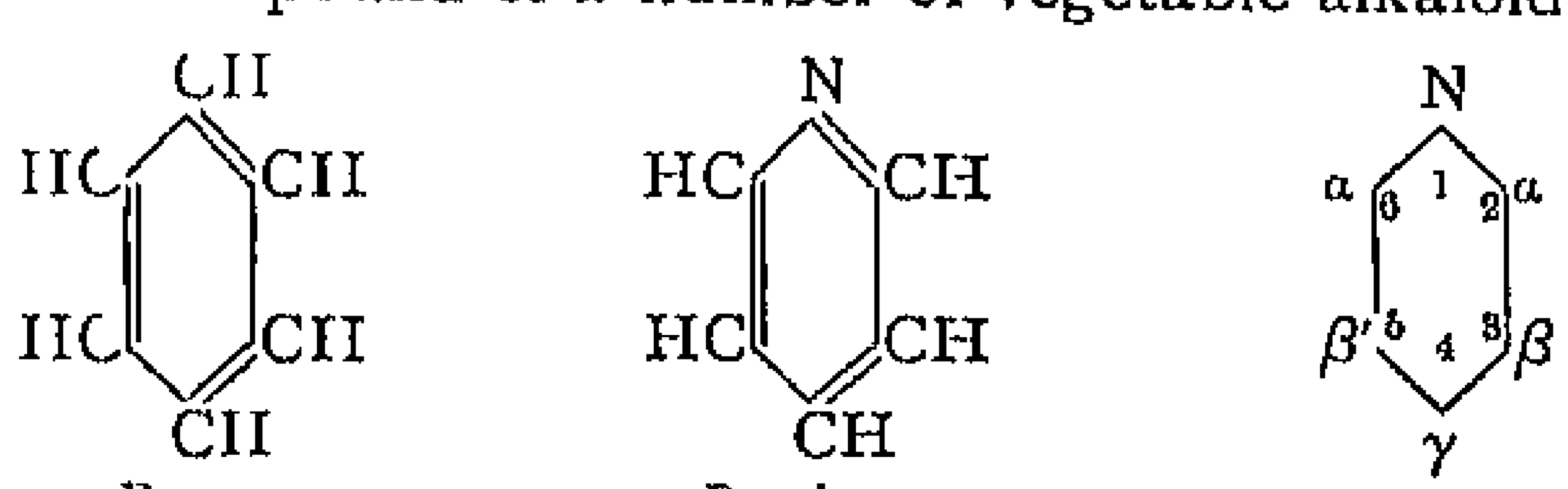


The xanthylium salts are closely related to the *benzopyrylium salts*, occurring in the anthocyanidin colouring matters of plants and berries (pp. 785 *et seq.*), and to the simple *pyrylium salts*[2] (III.), which may be regarded as the parent compounds of the whole group.

V

Pyridine Group

Pyridine and its derivatives contain a ring composed of five carbon atoms and one nitrogen atom. Pyridine can therefore be derived from benzene by replacing a trivalent CH-group by an atom of nitrogen. It is the parent compound of a number of vegetable alkaloids.



Benzene Pyridine

The above formula, proposed by Körner in 1869, offers a satisfactory explanation of the chemical behaviour of pyridine and its derivatives, and of the well-marked analogy between benzene and pyridine. It has been confirmed by several syntheses of pyridine compounds. As in the case of benzene, other formulæ have also been put forward.

The *possibilities of isomerism* among derivatives of pyridine are greater than with benzene, since not only does the relative position of the constituents to one another enter into the question, but also their position with regard to the nitrogen of the ring. Isomerides are

[1] F. Kehrmann, *Ann.*, 1910, 372, 287. [2] W. Dilthey and co-workers, *Ber.*, 1923, 56, 1012; 1924, 57, 1653. Also O. Diels and K. Alder, *Ber.*, 1927, 60, 716.

usually described by the use of numbers or letters, as indicated in the above formulæ. Theory predicts the existence of three mono-substitution products, and six or twelve di-substitution products, according as the substituents are similar or dissimilar.

Preparation, Properties and Uses of Pyridine.—Pyridine and certain of its homologues are produced by the action of heat on coal, peat, wood and various bituminous shales, and are thus present in the tar obtained by the dry distillation of these substances. They also occur in the unpleasant smelling product known as Dippel's oil, formed by the dry distillation of bones from which the fat has not been extracted. As will be seen later, pyridine also results from various alkaloids by the action of heat or alkalis, or by distillation with zinc dust at a red heat.

At present the chief source of pyridine and its homologues is coal tar. The fraction of the tar boiling between 80° and 170° ("light oil," see p. 368) used for the production of benzol is also worked up for pyridine bases, which are present to the extent of several units per cent. The oil is washed with dilute sulphuric acid in lead-lined vessels, and the bases are then liberated from the acid solution by addition of lime, and purified by rectification. The mixture of pyridine bases so obtained is used industrially in denaturing spirits, and as a solvent in the purification of crude anthracene (see p. 534).

Pyridine is a colourless liquid of unpleasant, penetrating smell, b.p. 114.5° and sp. gr. 1.0033 at 0°. It is miscible in all proportions with water, alcohol and ether, and forms salts with acids. Among the latter, the *ferrocyanide* and the *perchlorate*[1] are difficultly soluble and are used for the isolation and purification of pyridine.

The outstanding feature of pyridine is its great stability. Chromic acid, potassium permanganate and nitric acid do not attack it, and with sulphuric acid it is only converted into a sulphonic derivative at about 300°. Halogen substitution products are also only obtained with great difficulty; mercuration, on the other hand, proceeds readily.[2] Pyridine is a tertiary base, and when reduced with sodium and alcohol yields the secondary base, piperidine.

Pyridine sulphuric anhydride is prepared as a crystalline compound by drawing carefully regulated currents of air, impregnated respectively with sulphur trioxide (from warm oleum) and pyridine, into a barrel shaped receiver. The product is used for the preparation of sulphuric esters of phenolic compounds, in place of the mixture of chlorosulphonic acid and pyridine previously employed. It is much less sensitive to moisture than the usual sulphonating agents, and as a solid is more easily handled and weighed.

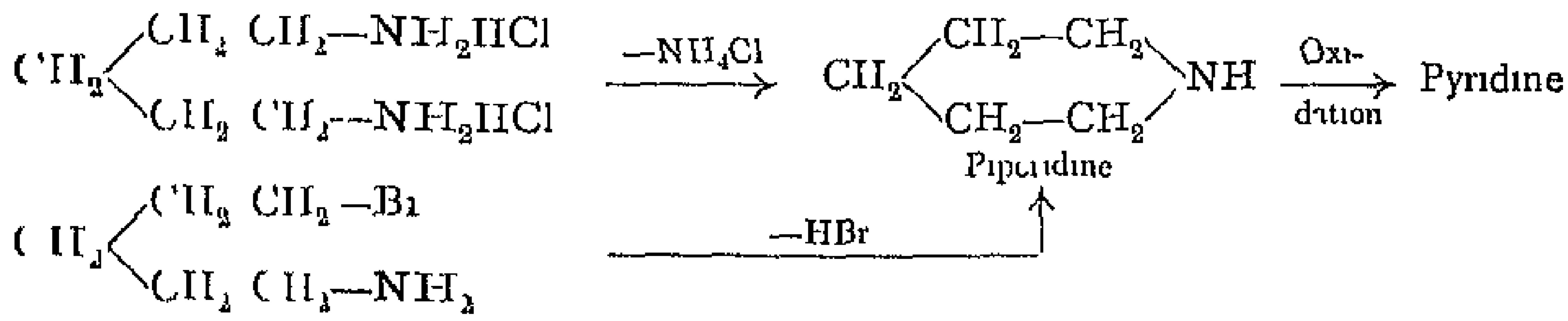
Syntheses of Pyridine and its Derivatives

1. The simplest method of building up a pyridine ring is from aliphatic compounds of the general formula

$$X—CH_2 . CH_2 . CH_2 . CH_2 . CH_2—NH_2$$

[1] *Ber.*, 1926, 59, 1074. [2] G. Sachs and R. Eberhartinger, *Ber.*, 1923, 56, 2223.

which may be converted into piperidine by ring formation, and by subsequent oxidation yield pyridine. Thus pentamethylene-diamine hydrochloride, on rapid heating, decomposes into ammonium chloride and piperidine. Similarly, normal ω-chloro- and ω-bromo-amylamine lose hydrogen halide on heating with alkali to give piperidine (Ladenburg)



These syntheses prove the constitution of piperidine and pyridine

2 A pyrogenic synthesis of pyridine, analogous to that of benzene from acetylene, occurs when acetylene and hydrogen cyanide are led through a tube heated to redness

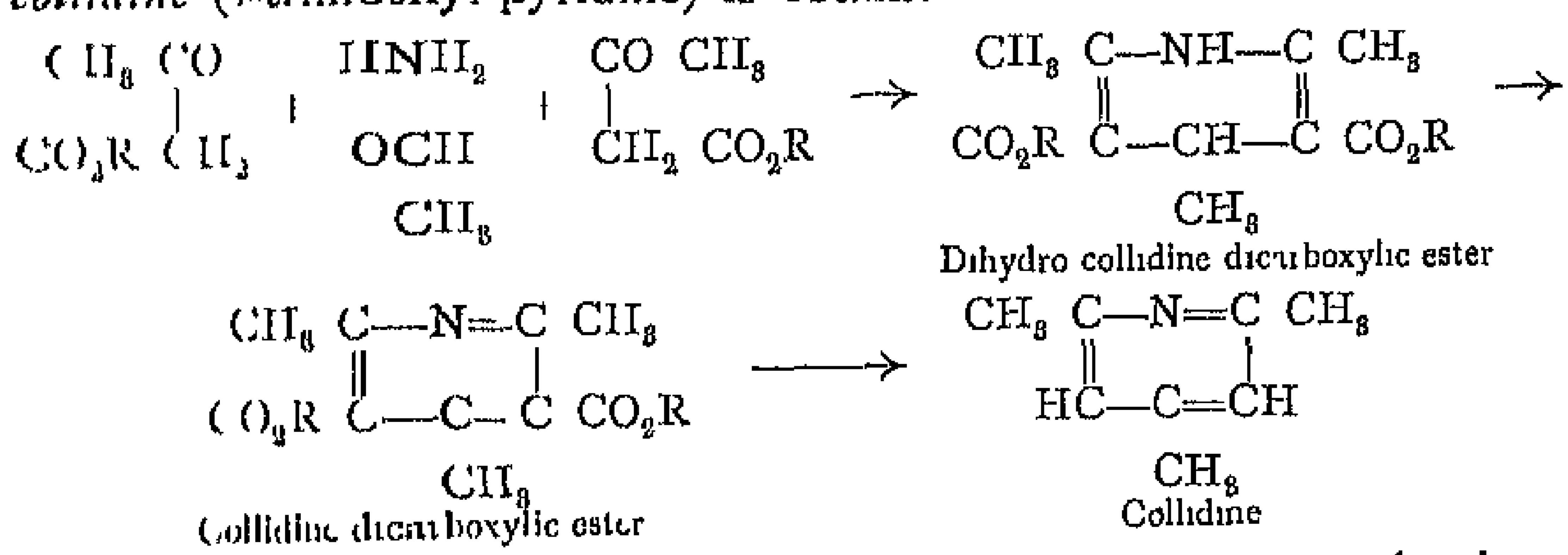
$$2C_2H_2 + CNH = C_5H_5N$$

3 The formation of pyridine derivatives from those of pyrrole, by extension of the ring, has already been mentioned on p 568

4 Compounds of the type of aldehyde-ammonia yield alkyl pyridines when heated alone or mixed with aldehydes or ketones

$$CH_3CHONH_3 + 3CH_3CHO = C_5H_3(CH_3)(C_2H_5)N + 4H_2O$$

5 A synthesis of general application is due to Hantzsch. Aldehyde-ammonia unites with acetoacetic ester to form *dihydro-collidine dicarboxylic ester*, which under the influence of nitrous acid loses two hydrogen atoms and is transformed into *collidine-dicarboxylic ester*. From this, by hydrolysis and elimination of carbon dioxide, *collidine* (s-trimethyl-pyridine) is obtained[1]



It may be assumed that in the first instance one molecule of aldehyde-ammonia (or aldehyde and ammonia) reacts with two molecules of acetoacetic ester, to form an alkylidene-acetoacetic ester and β-amino-crotonic ester, and that these compounds then interact

[1] A Hantzsch, *Ann.*, 1882, 215, 1; *Ber.*, 1885, 18, 2579. Compare also E Späth and G Burger, *Monats.*, 1928, 49, 265

with the production of a dihydro-pyridine derivative In confirmation of this, it has been shown that by working at low temperatures, at which the formation of dihydro-pyridine derivatives is retarded, the presence of alkylidene-acetoacetic ester can be proved[1]

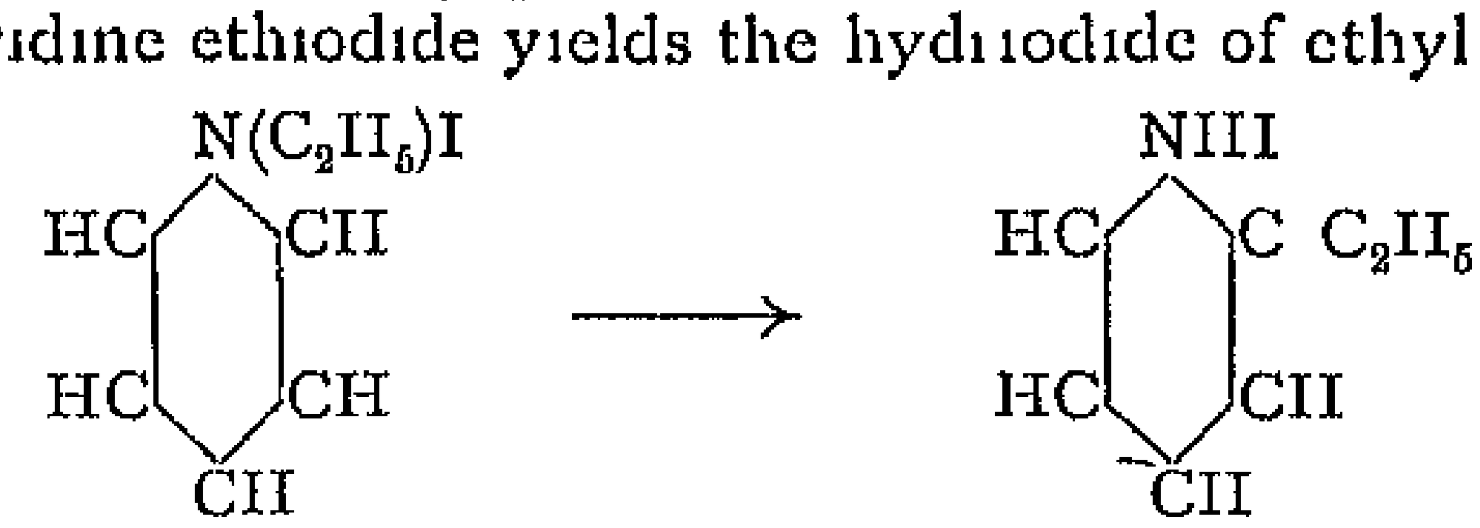
The above reaction may be varied by using other aldehydes in place of acetaldehyde, and other 1 3-diketones, such as acetyl-acetone or benzoyl-acetone, instead of the second molecule of acetoacetic ester

In addition, other reactions have been developed which permit a further extension of the above synthesis Among these are the formation of dihydro-pyridine derivatives by condensing 1 5-diketones with ammonia, and alkylidene-acetoacetic esters with β-amino-crotonic ester or ammonia derivatives of 1 3-diketones Alkylidene-malonic esters may also be employed in place of alkylidene-acetoacetic esters in the synthesis of pyridine compounds[1]

6 Pyridine derivatives can also be prepared from compounds of the pyrone group by treatment with ammonia, when the oxygen atom of the ring is replaced by the NH-group (see p 631)

7 The intramolecular rearrangement of the alkiodides, which has already been described in the case of aniline (p 380), pyrrole (p 570) and pyrazole (p 612), was observed by Ladenburg in the pyridine group, and offers a general means of converting pyridine into its homologues As a tertiary base pyridine unites with alkyl iodides to form the corresponding ammonium iodides When these are heated under pressure the alkyl radical migrates from nitrogen to a carbon atom of the nucleus, assuming either the α- or γ-position with respect to nitrogen, but never the β-position

Thus pyridine ethiodide yields the hydriodide of ethyl pyridine



8 Ammonia in the presence of acetic acid reacts with the oxymethylene-derivative of methyl *n* propyl ketone to form 2 n *propyl*-5 n *butyryl pyridine*, $C_5H_3(C_3H_7)(CO\ C_3H_7)N$ Similarly, oxymethylene acetone yields 2 *methyl* 5 *acetyl-pyridine*, $C_5H_3(CH_3)(COCH_3)N$[2]

General Behaviour of Pyridine Derivatives—The properties of pyridine itself have already been briefly described on p 638 The parent compound and its homologues are tertiary bases, which unite with one equivalent of an acid to form salts,[3] and also combine with inorganic salts such as mercuric chloride, and the sulphates of copper,

[1] Knoevenagel, *Ber*, 1903, 36, 2180 Rabe and Billmann, *Ber*, 1900, 33, 3806 [2] E Benary, *Ber*, 1927, 60, 914 [3] The methiodides and certain salts of pyridine and quinoline exist in modifications of different colour The polychromism of these derivatives is ascribed to **chromo-isomerism** Hantzsch and Hofmann, *Ber*, 1911, 44, 1776 Hantzsch, *ibid*, p 1783

zinc and cadmium, to give double salts of the type $C_5H_5N,HgCl_2$ and $(C_5H_5N)_2,(HgCl_2)_3$. As was indicated on p. 611, the composition and behaviour of these addition compounds illustrate the similarity between the pyridine and pyrazole series.

Pyridine and its derivatives unite directly with sodium bisulphite. The compounds so formed readily decompose with loss of ammonia and simultaneous opening of the ring.[1]

The strong resemblance between the pyridine and benzene series is illustrated by the following facts. Oxidising agents such as nitric acid and chromic acid attack neither benzene nor pyridine. Permanganate of potash converts pyridine homologues into carboxylic acids in the same manner as benzene homologues, the side chain being oxidised while the pyridine ring remains intact. From the constitution of the pyridine-carboxylic acids so obtained, conclusions may be drawn as to the number and position of the side chains originally present. Sulphuric acid converts pyridine and its homologues into sulphonic acids, although the action is slower than with benzene. The sulphonic group in these acids can be exchanged for the hydroxyl or cyano-group, by fusion with potash or potassium cyanide respectively. The resulting hydroxy-pyridines resemble the phenols in behaviour.

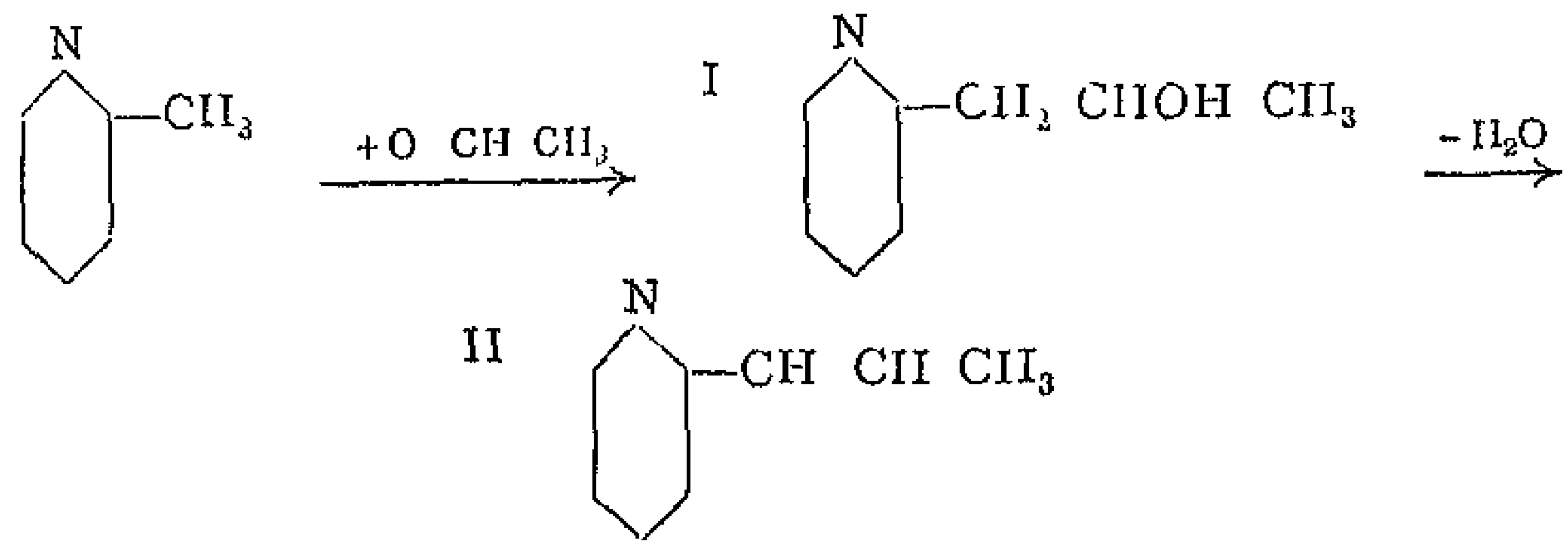
One notable difference between pyridine and benzene is that the pyridine ring can not be nitrated unless it is first substituted by some group such as OH or NH_2. According to Marckwald the resistance of pyridine to nitration is due to the strongly negative character of the nitrogen atom. Thus substituents always assume the β-position in the ring, *i.e.* the *meta*-position to nitrogen. The negative character of the nitrogen atom is also revealed in the α- and γ-chloro compounds of pyridine, the halogen of which is mobile, as in the *o*- and *p*-chloro-derivatives of nitrobenzene.

The reactivity of the halogens in α- and *γ-chloro-pyridines* is shown by the conversion of these compounds into *amino-pyridines* with ammonia, *pyridyl-hydrazines* with hydrazines, and *mercaptans* with potassium hydrosulphide. *Amino-pyridines* are also formed by the action of sodamide on pyridine and its homologues.[2]

The α- and *γ-methyl-pyridines* are also unusually reactive. According to experimental conditions they either condense with aldehydes to form products of the aldol type known as *alkines*, *e.g.* compound I, or else water is eliminated and oxygen-free, unsaturated bases, such as α-allyl-pyridine (II), are produced. The latter are generally termed *stilbazoles*.[3] As will be seen later, the α-allyl-pyridine obtained by this

[1] H. Bucherer and Schenkel, *Ber.*, 1908, 41, 1346. [2] O. Seide, *Ber.*, 1924, 57, 791. [3] Jacobsen and Reimer, *Ber.*, 1883, 16, 1082, 2602. Ladenburg, *Ann.*, 1898, 301, 117. Among aromatic aldehydes it appears that those substituted in the *o* position tend to yield alkines, whereas with *m*-substitution the tendency is to the formation of stilbazoles. Bach, *Ber.*, 1901, 34, 2229.

reaction is an intermediate product in the synthesis of the alkaloid conine Phthalic anhydride and phthalimide may also be employed in place of aldehydes in this condensation

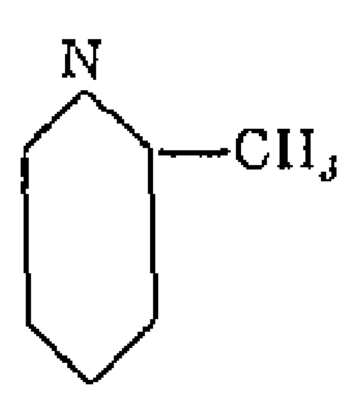


On reducing pyridine bases with sodium and alcohol, six atoms of hydrogen are taken up with the formation of piperidine bases More energetic reduction, by heating with hydrogen iodide, ruptures the ring with the production of paraffins, *e g* pyridine is converted into pentane

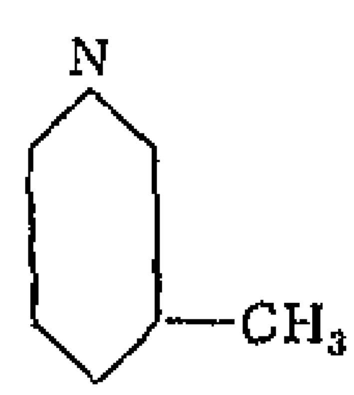
Homologues of Pyridine

The alkyl derivatives of pyridine mentioned above are found together with pyridine itself in bone oil and coal tar

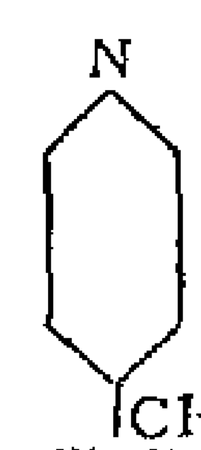
Methyl pyridines or Picolines, C_6H_7N All three possible isomerides are known They may be isolated from coal tar, or synthesised by the methods quoted above



α Picoline, b p 129 On oxidation yields picolinic acid



β Picoline, b p 142 143 On oxidation yields nicotinic acid



γ Picoline, b p 141 145 On oxidation yields iso nicotinic acid

Lutidines, C_7H_9N Nine isomerides are theoretically possible, three ethyl-pyridines and six dimethyl pyridines Of these, the three ethyl and five of the dimethyl derivatives are known α *Ethyl pyridine*, b p 184 5°, was obtained by the degradation of tropine β *Ethyl pyridine*, b p 166°, is formed by the decomposition of quinine and its degradation products

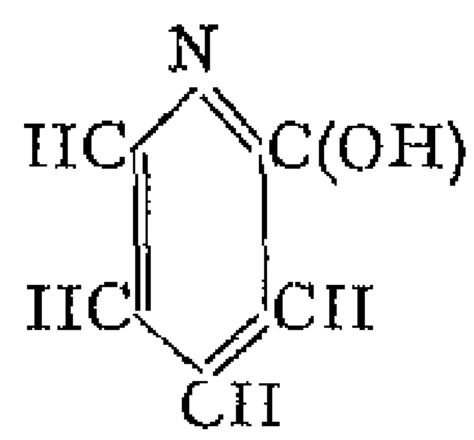
Collidines, $C_8H_{11}N$ No less than 22 isomerides are possible α *Methyl β'-ethyl pyridine* or *aldehydine*, b p 178°, is formed when aldehyde ammonia is heated in alcoholic solution α *Propyl pyridine* or *conyrine*, b p 166° to 168°, is closely related to the alkaloid conine, from which it is formed on distillation with zinc dust For *collidine*, see p 639

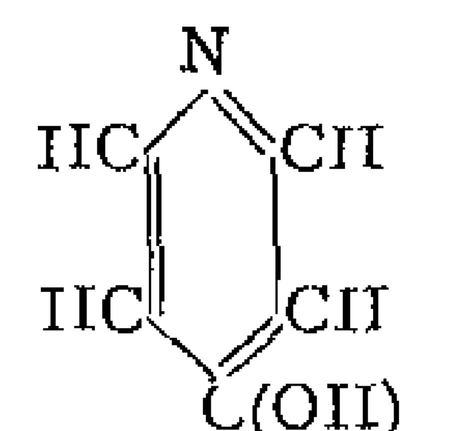
Hydroxy- and Amino pyridines

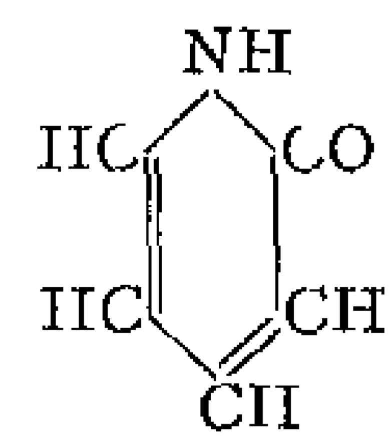
Hydroxy-pyridines may be compared with amino-phenols, which they resemble in yielding salts with bases as well as with acids

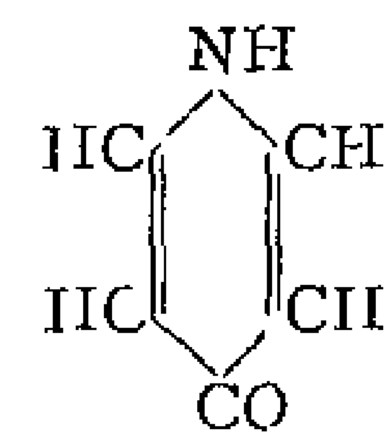
The three *hydroxy-pyridines* are high boiling substances which

crystallise well. They are best prepared from the corresponding carboxylic acids by elimination of carbon dioxide, and are also formed by direct hydroxylation[1] when pyridine vapour is led over powdered potassium hydroxide at 300° to 320°. A point of special interest is the *tautomerism* exhibited by α- and *γ-hydroxy-pyridines*. Each of these reacts in two ways: as a true hydroxy-pyridine, containing a phenolic hydroxyl group, and as a **pyridone**[2] or ketonic derivative of a dihydro-pyridine.


α Hydroxy-pyridine


γ Hydroxy-pyridine

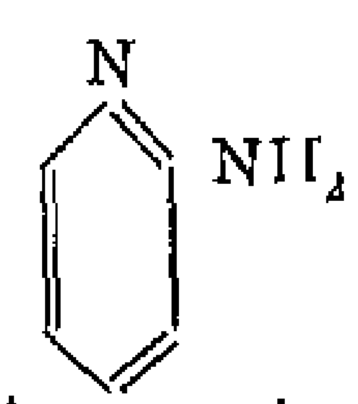

α Pyridone

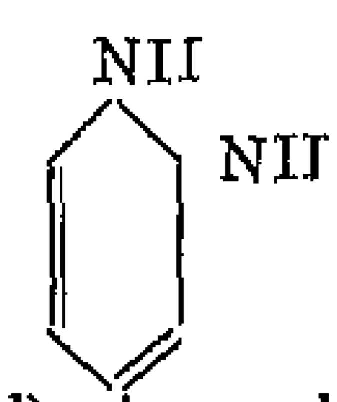

γ Pyridone

Whereas the free α- and γ-hydroxy-pyridines have so far only been isolated in one form, and it is still uncertain whether this corresponds to the hydroxy-pyridine or the pyridone type, the alkyl ethers of these compounds each exist in two forms of the constitution $C_5H_4(OR)N$ and $C_5H_4O(NR)$ respectively. β-Hydroxy-pyridine, on the other hand, reacts only as a phenol and never according to the pyridone type.

In the di- and trihydroxy-pyridines the basic character is entirely lost. These also show tautomerism of the above kind.

By analogy with the case of α-hydroxy-pyridine, it would be expected that α-amino-pyridine would give rise to two series of derivatives, corresponding to the tautomeric forms I and II, which may be described respectively as *α-amino-pyridine* and *α-pyridone-imide*:

I

α Amino-pyridine

II

α Pyridone-imide

In actual practice alkyl derivatives of both tautomeric forms are easily prepared.[3]

Pyridine-carboxylic Acids

Carboxylic acids of the pyridine series result, as stated above, from the oxidation of pyridine derivatives containing organic side-chains. Hence they are frequently obtained as degradation products of vegetable alkaloids, and a knowledge of their constitution is of great value in

[1] A. E. Tschitschibabin, *Ber.*, 1923, 56, 1879. [2] A. E. Tschitschibabin and co-workers, *Ber.*, 1924, 57, 1158; 1925, 58, 2650. [3] A. E. Tschitschibabin and co-workers, *Ber.*, 1924, 57, 1168; 1927, 60, 1607. For γ-amino-pyridine, see F. Koenigs, *Ber.*, 1924, 1179.

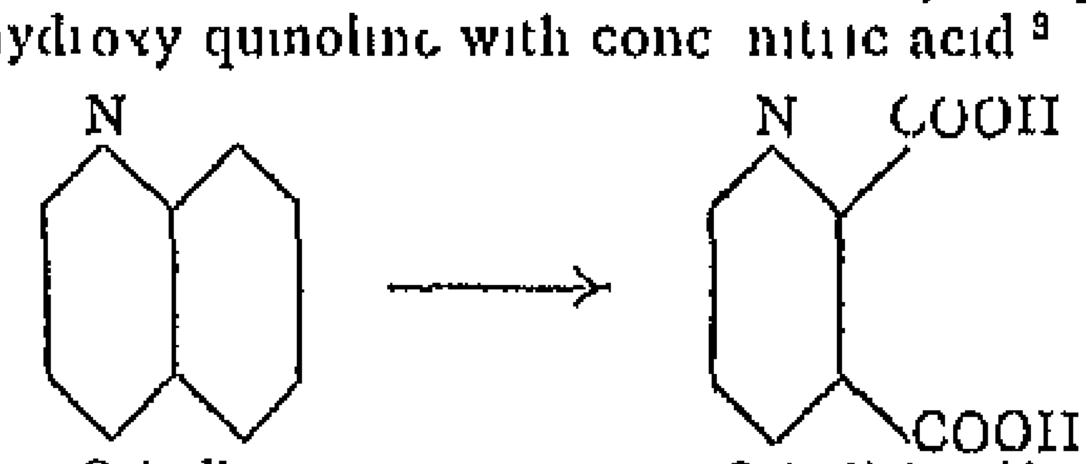
investigating the structure of the latter They are solid compounds, which possess both acidic and basic character, although the basic properties are not very evident in poly carboxylic acids When heated with lime, all these acids decompose into pyridine and carbon dioxide A carboxyl group in the α-position is particularly readily removed, and α-acids also differ from the others in giving a yellowish-red coloration with ferrous salts

Pyridine mono-carboxylic acids, $C_5H_4(COOH)N$, have already been mentioned on p 642 In **picolinic acid** (sublimes at 134° to 136°) the carboxyl group has been proved to occupy the α-position,[1] and this proof is one of the foundations upon which the absolute orientation of pyridine derivatives has been built up **Nicotinic acid**, or pyridine β carboxylic acid (sublimes at 228° to 229°), has been obtained by oxidation of various synthetic pyridine compounds, as well as of vegetable alkaloids (*e g*, nicotine, pilocarpine, hydrastine, berberine) The constitution of this acid follows from its formation by the action of heat on quinolinic acid Since the latter is obtained by the oxidation of quinoline (see later), it must contain its two carboxyl groups in the α- and β-positions The acid produced from quinolinic acid by loss of one molecule of carbon dioxide must therefore be an α- or a β-acid As the former structure has already been assigned to picolinic acid, it follows that nicotinic acid must be the β-compound **Isonicotinic acid**, m p 309°, results from the oxidation of various γ-substituted derivatives of pyridine In this case the carboxyl group must occupy the γ-position, since there are only three mono-carboxylic acids possible, and the α- and β-compounds have been shown to be represented by picolinic and nicotinic acids respectively

Coramine, $C_5H_4(CO\cdot NEt_2)N$, the diethylamide of pyridine-β-carboxylic acid, resembles camphor in many of its physiological properties In some respects its action is more powerful than that of camphor, *e g*, on the blood pressure and respiration, in its stimulating action on the heart and as an antidote to morphine Hence it is employed medicinally[2]

Each of the six possible *pyridine dicarboxylic acids*, $C_5H_3(COOH)_2N$, is known, and their constitutions have been established mainly by the researches of Hantzsch and his co-workers

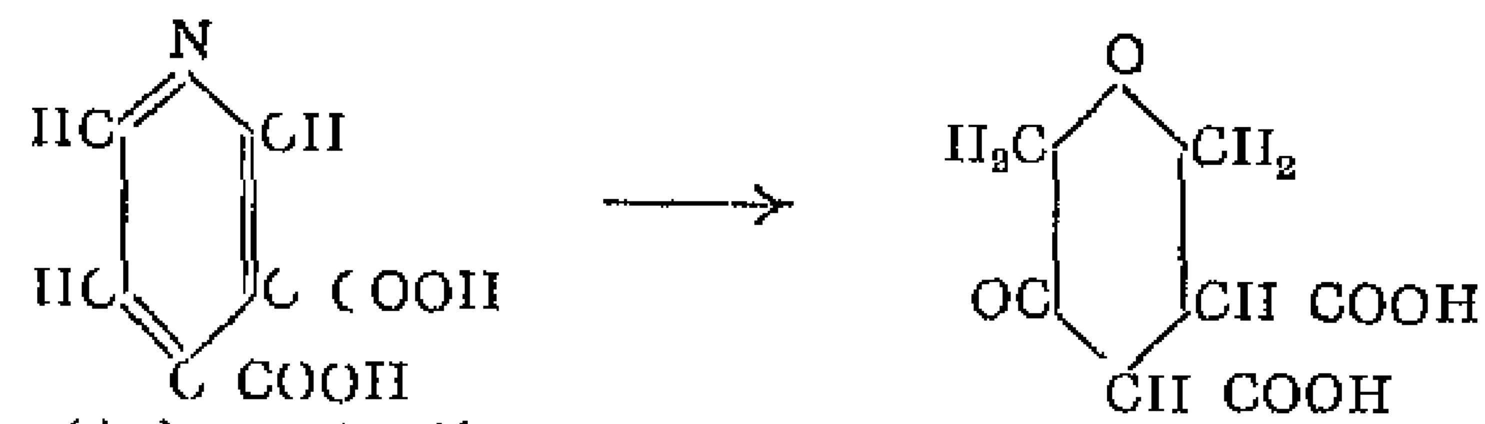
Quinolinic acid, *αβ pyridine dicarboxylic acid*, is formed by the oxidation of quinoline, from which its constitution follows It may be prepared in very good yield by oxidising 8 hydroxy quinoline with conc nitric acid[3]



Quinoline Quinolinic acid

[1] Skraup and Cobenzl, *Monats*, 4, 436 [2] Thannhauser and Fritzel, C, 1924, II, 2187
[3] E Sucharda, *Ber*, 1925, 58, 1727

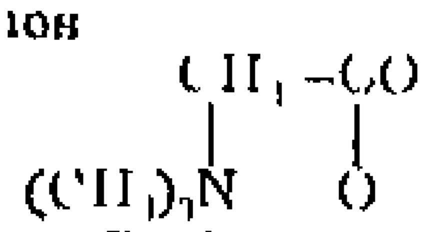
It melts at 192°, with evolution of carbon dioxide and conversion into nicotinic acid **Cinchomeronic acid**, *β γ pyridine dicarboxylic acid*, is obtained as a degradation product of various cinchona alkaloids, such as quinine and cinchonine It melts at 258 to 259°, with evolution of carbon dioxide Sodium amalgam converts it into the nitrogen free *cinchonic acid*, a reaction which appears to be the reverse of that described on p 631, by which derivatives of pyrone pass into those of pyridine



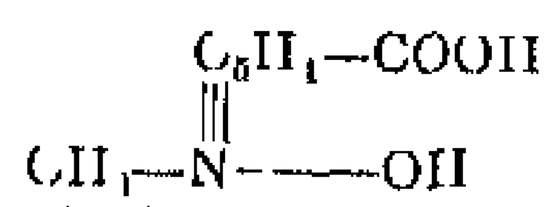
Cinchomeronic acid   Cinchonic acid

Lutidinic acid, *α γ pyridine dicarboxylic acid*, melting point		235°
Dinicotinic acid, *β β'*	,, ,, ,,	323
Isocinchomeronic acid, *α β'*	,, ,, ,,	236 to 237°
Dipicolinic acid, *α α'*-	,, ,, ,,	226°

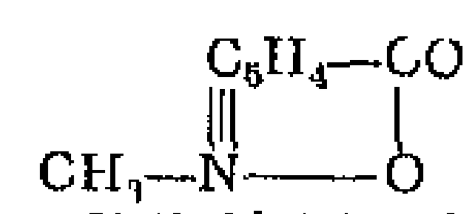
The higher acids of this series cannot be described here It may, however, be mentioned that pyridine carboxylic acids give rise to an interesting type of compound, the constitution of which resembles that of betaine (see pp 213 and 218), their methyl hydroxides are unstable and immediately part with water to form betaines



Betaine



Metho hydroxide of pyridine carboxylic acid



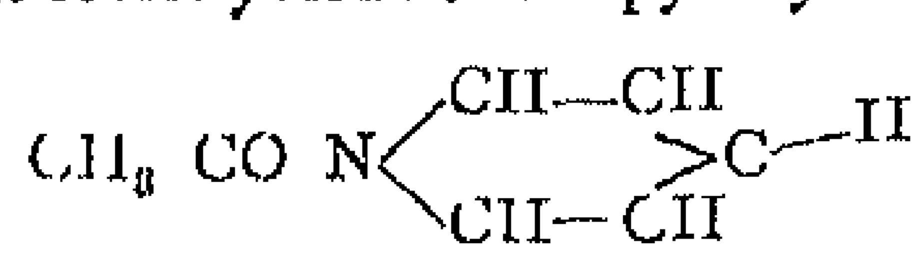
Methyl betaine of pyridine carboxylic acid

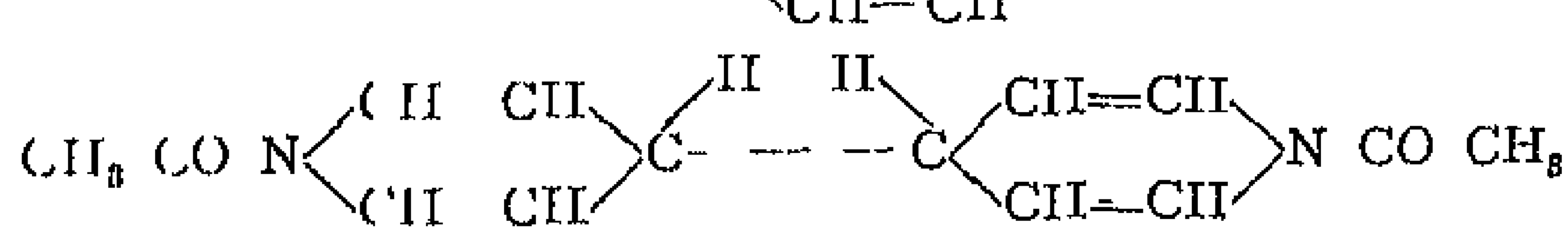
Hydro-pyridine Derivatives

Derivatives of dihydro pyridine are produced synthetically, as stated on p 639, by the action of ammonia on diketo compounds

On reducing pyridine and its derivatives by means of sodium and alcohol, six atoms of hydrogen are taken up and hexahydro-compounds produced, 1 4-dihydropyridine being formed as an intermediate product[1]

The reduction of pyridine with zinc dust and acetic anhydride leads to the formation of **NN'-diacetyl-(tetrahydro γγ'-dipyridyl)** of formula II below This is a crystalline compound, m p 124° to 125°, the production of which is explained by assuming that the reagents first attack the nitrogen atom with the temporary formation of the radical (I), which by union with itself yields the dipyridyl derivative (II)[2]

I 

II 

[1] B D Shaw, J C S, 1925, 215 [2] O Dimroth and co workers, *Ber*, 1921, 54, 2934, 1923, 56, 1223

Piperidine, hexahydro-pyridine, $CH_2\left\langle\begin{array}{l}CH_2-CH_2\\CH_2-CH_2\end{array}\right\rangle NH$, was first prepared from the alkaloid piperine, present in pepper, by heating with alkali. Its formation by synthetic methods, and by the reduction of pyridine (with sodium and alcohol or by electrolytic means), has already been mentioned in the foregoing pages.[1] It is a colourless liquid of peculiar ammoniacal smell, miscible in all proportions with water, alcohol, ether and benzene. It boils at 105°, solidifies at −17°, and is of sp. gr. 0.88 at 0°. Whereas pyridine is a weak tertiary base of aromatic character, piperidine is a strong secondary base, the entire behaviour of which classes it with the aliphatic amines. The imino-hydrogen atom of piperidine may be replaced by different radicals (alkyl, acyl, nitroso groups, etc.), and numerous derivatives have thus been prepared which cannot be described here. On being heated at 300° with concentrated sulphuric acid, at 250° with nitrobenzene or at 180° with silver acetate, piperidine becomes oxidised to pyridine.

Alkaloids derived from piperidine are treated in a later chapter.

Tetrahydro-pyridine-3-*aldehyde* and *piperidine*-3-*aldehyde* have been prepared synthetically.[2]

As has been shown by J. v. Braun, alkylation of the carbon atoms strengthens the structure of the piperidine ring. This effect becomes apparent on the introduction of a single methyl group.[3]

Methods of Opening the Piperidine Ring

A number of methods are available for rupturing the piperidine ring, processes which are in a sense a reversal of the syntheses described on pp. 638 *et seq.*

1. *By Oxidation.*—Under the influence of oxidising agents, such as hydrogen peroxide, the piperidine ring is comparatively easily broken between the nitrogen atom and an adjacent carbon atom, with the formation of δ-amino-valeraldehyde.[4]

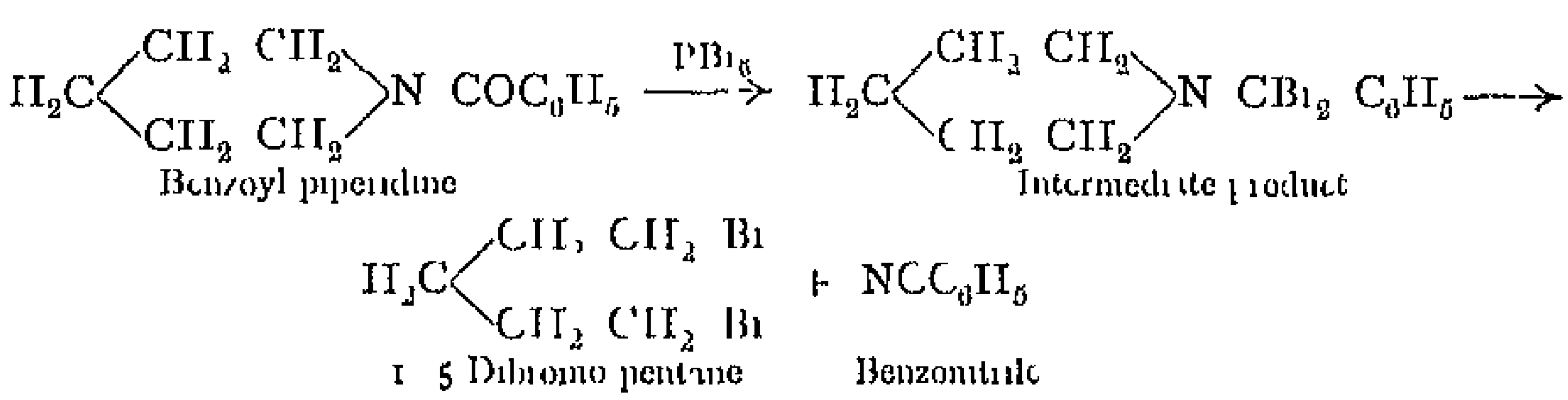
$$CH_2\left\langle\begin{array}{l}CH_2-CH_2\\CH_2-CH_2\end{array}\right\rangle NH + O = CH_2\left\langle\begin{array}{l}CH_2\cdot CHO\\CH_2\cdot CH_2\cdot NH_2\end{array}\right.$$

The opening of the ring is effected even more readily by the action of potassium permanganate on N-acylated piperidine derivatives. In this way, benzoyl-piperidine, $C_5H_{10}N(COC_6H_5)$, yields benzoyl-δ-amino-valeric acid. On the other hand, when N-alkyl piperidines are

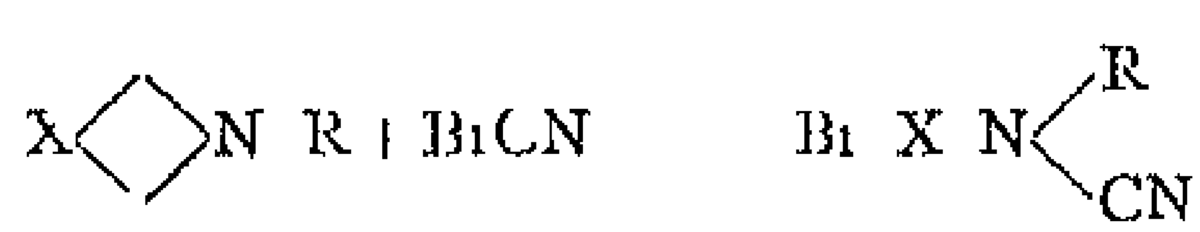
[1] For the preparation of chemically pure piperidine, compare Vorländer, *Ann.*, 1906, 345, 277.
[2] A. Wohl and Losanitsch, *Ber.*, 1907, 40, 4685. [3] J. v. Braun and F. Zobel, *Ber.*, 1926, 59, 1786. [4] Wolffenstein, *Ber.*, 1892, 25, 2777. On reduction with zinc and hydrochloric acid, amino-valeraldehyde is converted back into piperidine.

treated with hydrogen peroxide they take up an oxygen atom to form alkyl-piperidine oxides,[1] $CH_2<\begin{smallmatrix}CH_2—CH_2\\CH_2—CH_2\end{smallmatrix}>N<\begin{smallmatrix}Alk\\O\end{smallmatrix}$

2 *By Means of Phosphorus Halides.*—The work of J. v. Braun[2] has shown that acyl derivatives of piperidine are very easily attacked by phosphorus pentachloride or pentabromide. Under chosen conditions the resulting 1 : 5-dichloro pentane or 1 : 5-dibromo pentane is obtained in so good a yield that the reaction can be used as a means of preparing these halogen compounds.[3]



3 *By Means of Cyanogen Bromide.*—J. v. Braun has also discovered that substitution products of piperidine, and other cyclic tertiary bases of the general type $X<>N.R$, are disrupted by cyanogen bromide[4] according to the following equation to give brominated cyanamides $Br.XN(CN).R$,

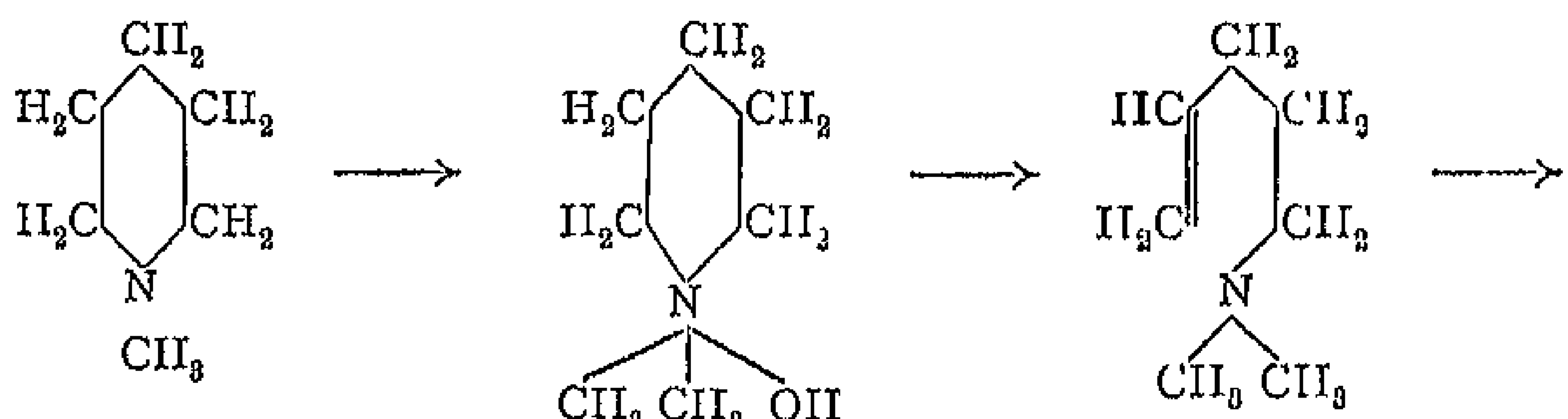


provided that the alkyl group R is not removed from the molecule. Such a cyanamide derivative may undergo hydrolysis to a brominated secondary amine, $Br.X.NH.R$. This constitutes the simplest available method of opening a ring containing nitrogen, and may also be employed with success in cases where (as with the aromatic derivatives of piperidine) the following method (4) cannot be applied.

4. *By Means of Exhaustive Methylation.*—A method of opening the piperidine ring, with simultaneous loss of nitrogen, is by "exhaustive methylation." This series of reactions, first used by A. W. Hofmann in the case of piperidine, was correctly interpreted by Ladenburg and later applied by other investigators to a large number of cyclic bases (see p. 578). It has been the classical weapon of attack in determining the constitution of the majority of vegetable alkaloids, and may

[1] Auerbach and Wolffenstein, *Ber.*, 1901, **34**, 2411; 1911, **44**, 1161. [2] *Ber.*, 1904, **37**, 2915, 3210. [3] The amino- and imino-chlorides (or bromides) which may be produced during this reaction cannot be discussed here. The above 1 : 5 dihalogen compounds are readily converted into the dicyano derivatives, and by further hydrolysis into pimelic acid. This provides a convenient method of preparing pimelic acid. J. v. Braun, *Ber.*, 1904, **37**, 3588. [4] J. v. Braun, *Ber.*, 1907, **40**, 3914; 1909, **42**, 2219; 1911, **44**, 1252.

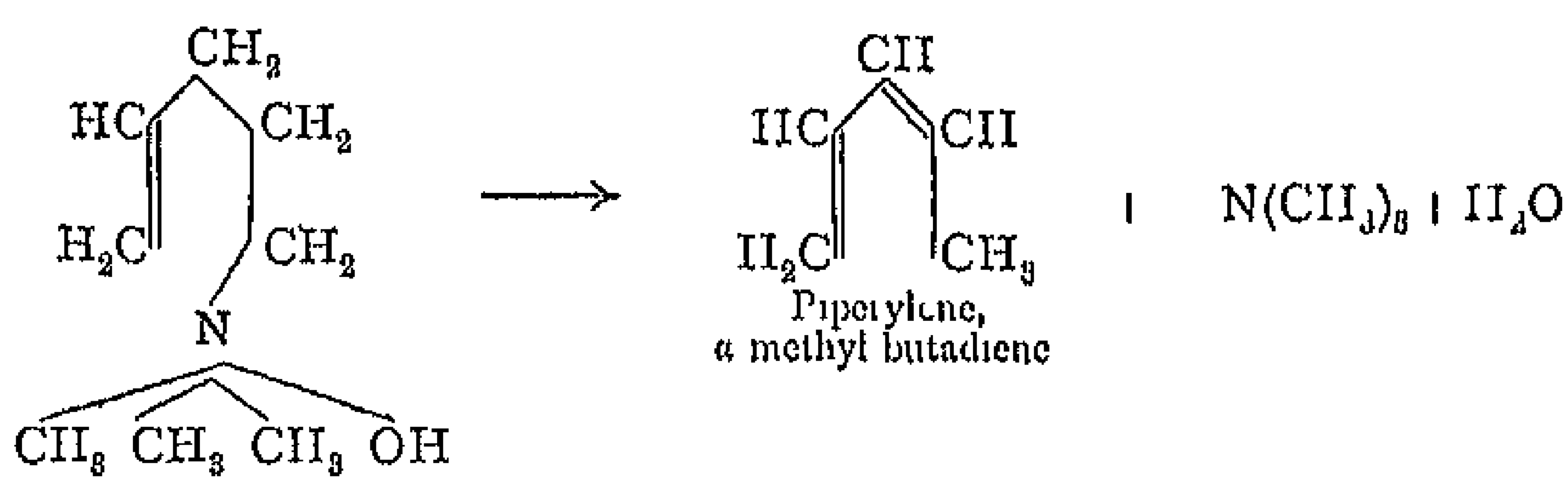
therefore be treated in some detail The operations are as follows Piperidine, as a secondary base, can be methylated at the nitrogen atom by means of methyl iodide The methyl piperidine so obtained unites with methyl iodide to form dimethyl-piperidinium iodide, and this by treatment with moist silver oxide is converted into dimethyl-piperidinium hydroxide The latter on dry distillation breaks up into water and a compound frequently described as dimethyl-piperidine,[1] but correctly named Δ^1-pentenyl-dimethylamine Being a tertiary base, this substance also unites with methyl iodide to form a substituted ammonium iodide, which when converted as before into the ammonium hydroxide and submitted to dry distillation yields trimethylamine, water and a hydrocarbon, α-methyl-butadiene, of the formula C_5H_8 (see p 115)



Methyl piperidine

Dimethyl-piperidinium hydroxide

Δ^1 Pentenyl-dimethyl amine



Piperylene, α methyl butadiene

It has been mentioned on p 579 that the addition product formed by Δ^1-pentenyl-dimethylamine with hydrochloric acid readily isomerises into the methochloride of 1 2-dimethyl-pyrrolidine, thus forming a connection between the pyridine and pyrrole series

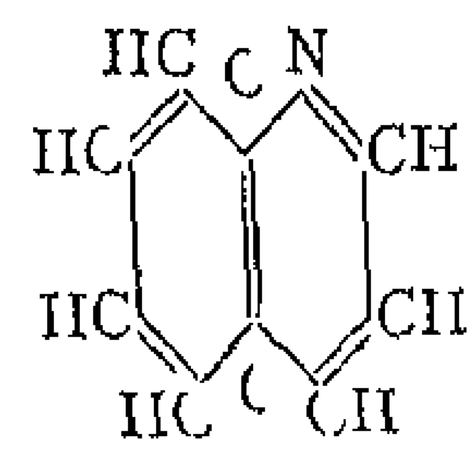
5 *By Reduction* — When heated to 300° with hydriodic acid, piperidine decomposes into *n*-pentane and ammonia

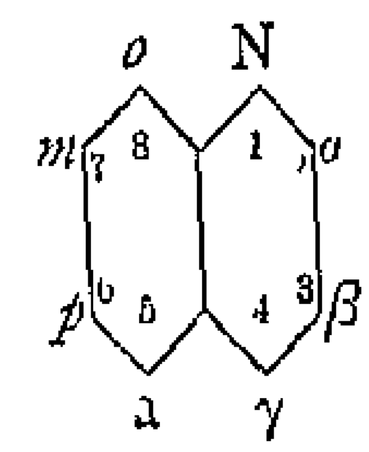
[1] This name arose from the fact that Hofmann regarded the base as a homologue of piperidine Unfortunately this incorrect method of description has since come into use for the numerous products obtained by the exhaustive methylation of pyrrolidines, substituted piperidines and many alkaloids It is desirable that the unsaturated amines produced in this manner should be given names appropriate to their constitution, by means of which they may be distinguished from the isomeric cyclic bases with whose names they have wrongly been associated

VI

Quinoline, Isoquinoline and Acridine Group

Quinoline is related to pyridine in the same manner as naphthalene to benzene, and may be looked upon as $\alpha\beta$ benzo-pyridine, or a naphthalene in which one CH-group in the α-position is replaced by a nitrogen atom





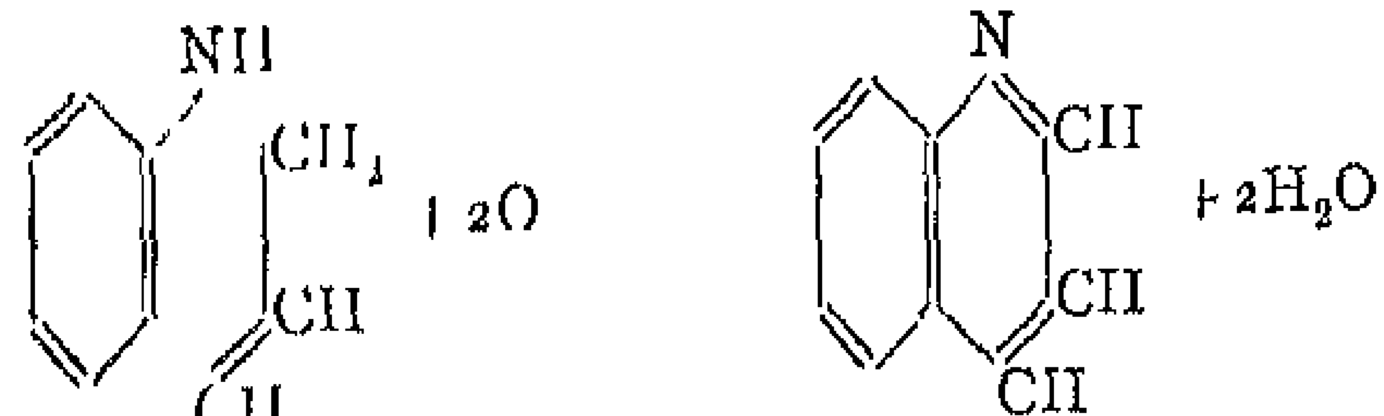
In this series the number of *isomeric substitution products* is very large A glance at the formula for quinoline reveals the fact that no two hydrogen atoms are similarly situated with respect to the nitrogen atom The position of substituents is best represented by making use of the above numbering as suggested by Richter Substituents in the pyridine nucleus are also frequently indicated by means of the Greek letters α, β, γ, and in the benzene nucleus by the prefixes *o*-, *m*-, *p*-, and *ana*-

Quinoline is found in coal tar and bone oil, and is produced by distilling many alkaloids—particularly the cinchona alkaloids—with potassium hydroxide It is a colourless, oily liquid which boils at 240°, solidifies at −19 5°, and is of sp gr 1 081° at 0° It possesses a peculiarly characteristic smell, is almost insoluble in water and dissolves readily in alcohol, ether and the majority of organic solvents In chemical properties it resembles pyridine, and like the latter is a tertiary base With acids it unites to form salts, of which the bichromate, $(C_9H_7N)_2H_2Cr_2O_7$, is sparingly soluble

Synthesis of Quinoline and its Derivatives

The formula given above is confirmed by a number of syntheses of quinoline, among which the following may be mentioned

1 The first synthesis of quinoline was effected in 1879 by passing the vapour of allyl-aniline over lead oxide heated to redness (Konigs)



Allyl aniline Quinoline

2. Preparations of quinoline and of those derivatives substituted in the benzene nucleus are based almost exclusively on *Skraup's synthesis*. This consists in heating an aromatic amino compound with glycerol and sulphuric acid, in the presence of nitrobenzene or arsenic acid[1] as oxidising agent. Quinoline itself is obtained in this way by heating a mixture of aniline, glycerol and nitrobenzene with concentrated sulphuric acid.

The mechanism of the reaction is in all probability as follows. Under the dehydrating influence of sulphuric acid, glycerol is first converted into acrolein; this condenses with aniline to form acrolein-aniline, which is then oxidised with the production of a pyridine ring.

$$\underset{\text{Glycerol}}{CH_2OH{-}CHOH{-}CH_2OH} \xrightarrow{-2H_2O} \underset{\text{Acrolein}}{CH_2{=}CH{-}CHO} \xrightarrow{C_6H_5NH_2}$$

$$\underset{\text{Acrolein-aniline}}{CH_2{=}CH{-}CH{=}NC_6H_5} \xrightarrow{\text{Oxidation}} \text{Quinoline}$$

This reaction has proved extraordinarily fruitful, since the place of aniline may be taken by its homologues, halogen and nitro-substitution products, and also by amino-carboxylic acids, amino-sulphonic acids and amino-phenols, thus enabling a great variety of quinoline derivatives to be prepared containing substituents in the benzene nucleus. In addition, aniline may be replaced by naphthyl-amines, with the formation of naphtho-quinolines; and by making use of diamines, two pyridine rings may be linked on to the benzene nucleus, the compounds so obtained being known as *phenanthrolines*.

The preparation of alizarin blue described on p. 543, which was known before the discovery of Skraup's synthesis, is another example of this method of forming a quinoline derivative.

3. *The quinaldine syntheses* of Doebner and Miller[2] are also based on Skraup's synthesis. Quinaldine (α-methyl quinoline) was obtained by heating acetaldehyde (paraldehyde) with aniline and concentrated sulphuric or hydrochloric acid. By using other aldehydes of the formula $R \cdot CH_2 \cdot CHO$ in place of acetaldehyde, and other aromatic amines instead of aniline, it is possible to prepare in this manner a great number of quinoline derivatives. The mechanism of the reaction has yet to be satisfactorily explained.

$$C_6H_5NH_2 + 2CH_3 \cdot CHO \longrightarrow \underset{\text{Quinaldine}}{C_9H_6(CH_3)N} + 2H_2O + H_2$$

[1] Skraup, *Ber.*, 1881, **14**, 1002; *Monats.*, 1880, **1**, 316; 1881, **2**, 141; *Ber.*, 1896, **29**, 703. The somewhat vigorous reaction may be modified and the yield increased by the addition of boric acid and ferrous sulphate, F. W. Cohn, *J. A. C. S.*, 1930, 3685.

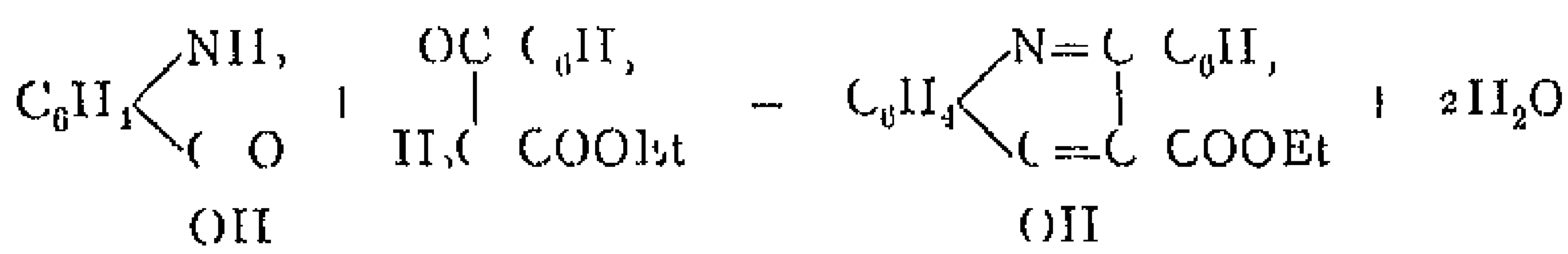
[2] *Ber.*, 1892, **25**, 2072, 2864; 1896, **29**, 59; 1903, **36**, 4013. W. Borsche, *Ber.*, 1908, **41**, 3884.

γ-Methylquinoline or lepidine[1] is produced by the condensation of acetaldehyde with aniline in the presence of alumina at high temperatures.

4. Another synthesis of general application is that discovered by Friedländer,[2] who obtained quinoline by condensing *o*-amino-benzaldehyde with acetaldehyde:

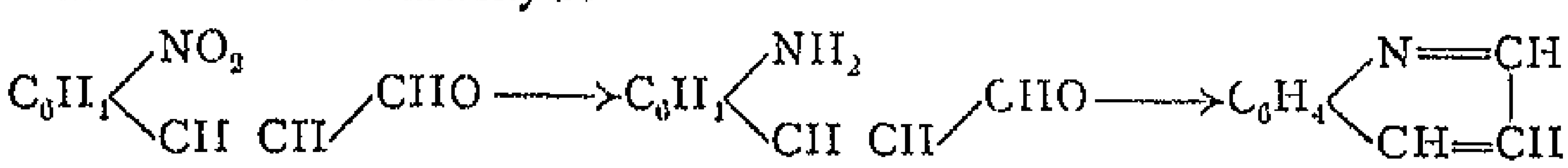
Once again, the *o*-amino-benzaldehyde may be replaced by its substitution products, by *o*-amino-benzoketones or *o*-amino-benzoic acid, and in place of acetaldehyde other compounds containing the group $CH_2 \cdot CO$ may be used, *i.e.* aldehydes, ketones, acetoacetic ester and malonic ester.

Anthranilic acid condenses with benzoyl-acetic ester, for example, according to the equation:



4-Hydroxy-2-phenyl-quinoline-3-carboxylic ester

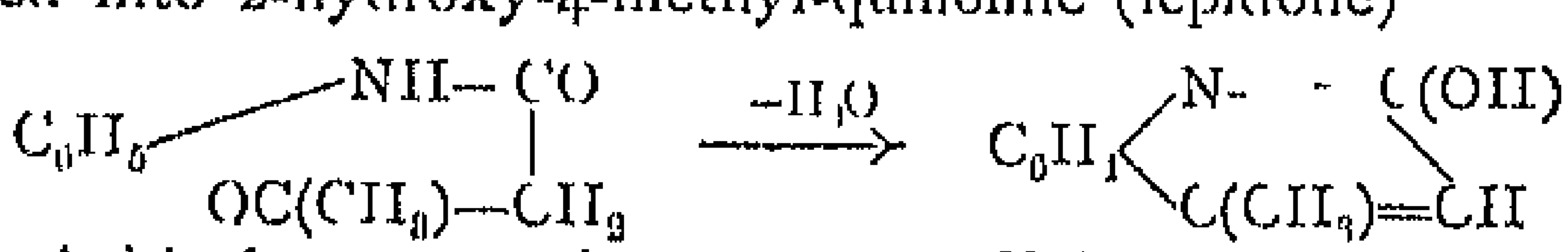
5. Baeyer and Drewsen prepared quinoline by the reduction of *o*-nitro-cinnamic aldehyde:



This reaction gives a clear insight into the constitution of quinoline, and affords further proof that it is an ortho-derivative of benzene.

6. Hydroxy-derivatives of quinoline may be synthesised from the products formed by the condensation of β-ketonic acids with aromatic amines. By the interaction of acetoacetic ester and aniline, for example, two different products are obtained according as the reaction proceeds in the cold or at a moderate temperature. In the former case β-phenyl-amino-crotonic ester (anil of acetoacetic ester) is formed and in the latter the anilide of acetoacetic acid (Knorr).

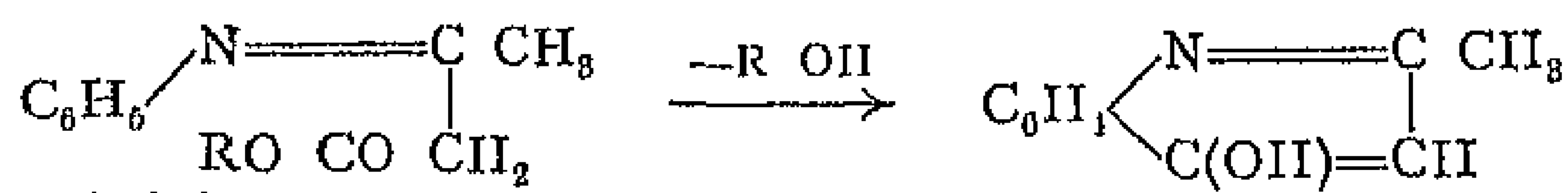
It has been shown by Knorr[3] that the anilide of acetoacetic acid loses water on treatment with concentrated sulphuric acid and is converted into 2-hydroxy-4-methyl-quinoline (lepidone):



Anilide of acetoacetic acid — 2-Hydroxy-4-methyl-quinoline

[1] A. E. Tschitschibabin und M. P. Oparina, *Ber.*, 1927, 60, 1873. [2] *Ber.*, 1882, 15, 2572; 16, 1833; 1892, 25, 1752. [3] *Ann.*, 236, 69, 112.

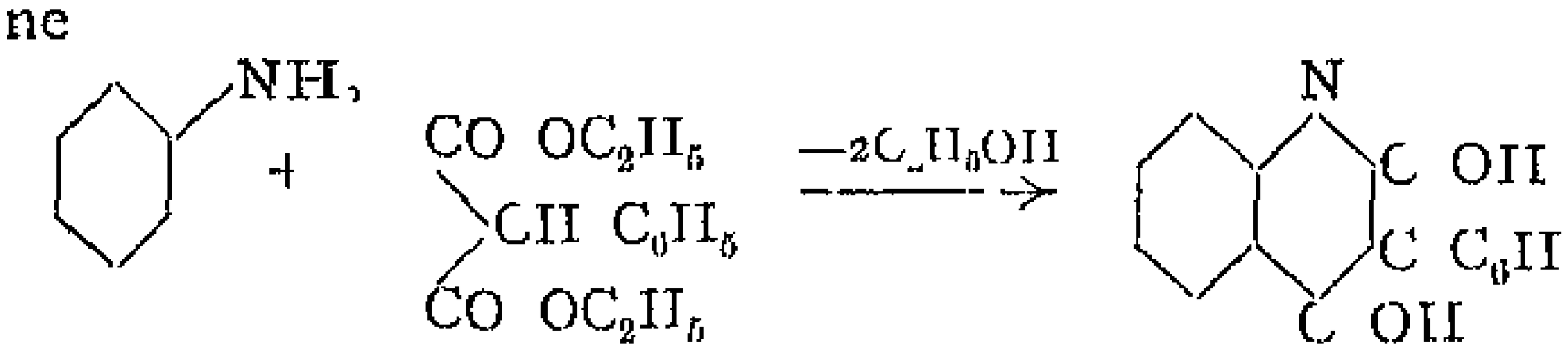
When the anil of acetoacetic ester is heated to 250° it yields 2-methyl-4-hydroxy-quinoline



Anil of acetoacetic ester — 2-Methyl-4-hydroxy-quinoline

This reaction can also be carried out by using benzoyl-acetic ester, acetone dicarboxylic ester, and other similar compounds in place of acetoacetic ester, and with homologues of aniline and also phenylene diamine as substitutes for aniline

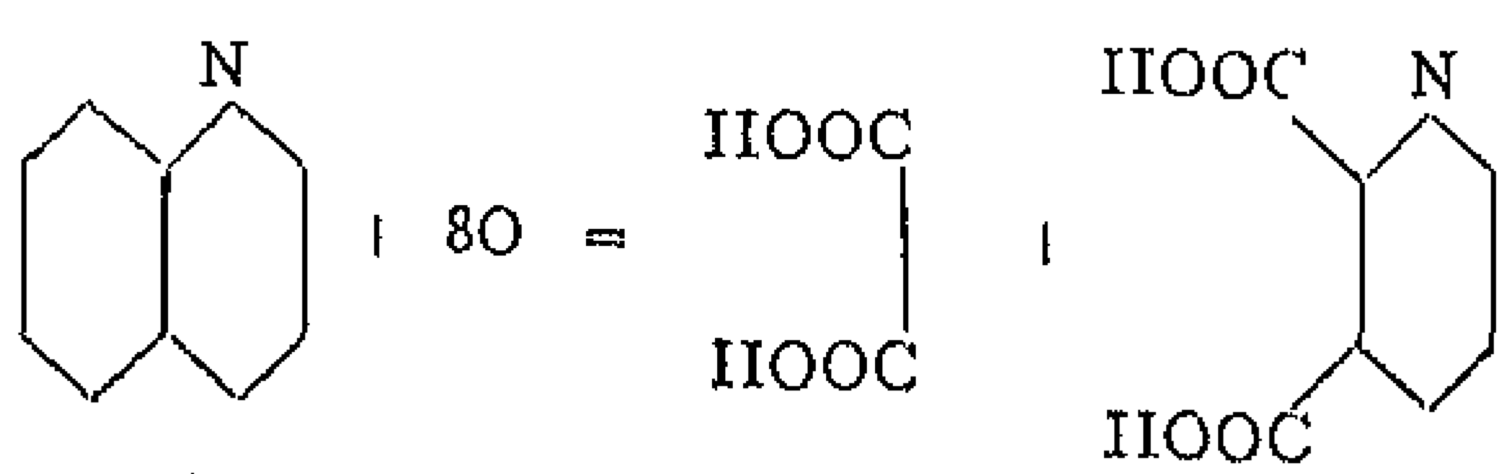
7 A simple synthesis of 2 4-dihydroxy-quinolines consists in heating alkylated and arylated malonic esters with aromatic amines[1] Thus phenyl-malonic ester and aniline yield 3-phenyl-2 4-dihydroxy-quinoline



Properties of Quinoline

Quinoline and its homologues are liquids of characteristic odour, sparingly soluble in water, but dissolving readily in alcohol and ether Being substituted derivatives of pyridine, they resemble the latter closely in chemical behaviour

A point of considerable importance is the *behaviour of quinoline on oxidation*,[2] as this has provided valuable confirmation of the structure deduced from synthesis (see above) When quinoline is oxidised by potassium permanganate it yields quinolinic acid together with oxalic acid



Quinoline — Oxalic acid — Quinolinic acid

Whilst the syntheses already quoted indicate that quinoline is an ortho-disubstituted derivative of benzene, this degradation shows it to be a 2 3-disubstitution product of pyridine, thus completing the proof of the quinoline formula

Similarly, in the homologues of quinoline the benzene nucleus is less stable to oxidation with permanganate than the pyridine nucleus,

[1] P Baumgarten and W Kärgel, *Ber*, 1927, 60, 832 [2] For the degradation of quinoline by reduction, see H Emde, *Ann*, 1912, 391, 88

and pyridine carboxylic acids are again formed. On the other hand, oxidation with chromic acid in sulphuric acid solution attacks the side chain, leaving the quinoline nucleus intact and yielding quinoline carboxylic acids.

Quinoline, like pyridine, is not easily nitrated. The first products to be formed are 5- and 8-*nitro-quinolines*, which on further nitration yield 5,7- and 6,8-*dinitro-quinolines*.[1] The sulphonation of quinoline, in the same manner, leads only to substitution in the benzene nucleus. Sulphonic acids, in which the sulphonic group is attached to the pyridine ring, are obtained by oxidation of thio-quinolines with nitric acid, or from quinolines containing chlorine in the pyridine nucleus, by double decomposition with alkali sulphite.[2] As with the chloro-pyridines (p. 641), only the chlorine atoms in the 2- and 4-positions in chloro-quinolines can be exchanged for basic radicals.

The 2- and 4-homologues of quinoline behave towards aldehydes in the same manner as those of pyridine (see pp. 641 *et seq.*).

As will be described in more detail under the hydroquinolines, hydrogen very readily adds on to the pyridine nucleus of quinoline.

Only a few of the large number of quinoline derivatives known can be treated here. Certain of these compounds are used in medicine or as dye-stuffs.

Homologues of Quinoline

All of the seven theoretically possible methyl-quinolines are known. The four of these containing the methyl group in the benzene nucleus are generally termed *toluquinolines*.

Quinaldine, 2-*methyl-quinoline*, $C_9H_6(CH_3)N$, is found with quinoline in coal tar, and can be prepared synthetically by the foregoing methods. It boils at 247°.

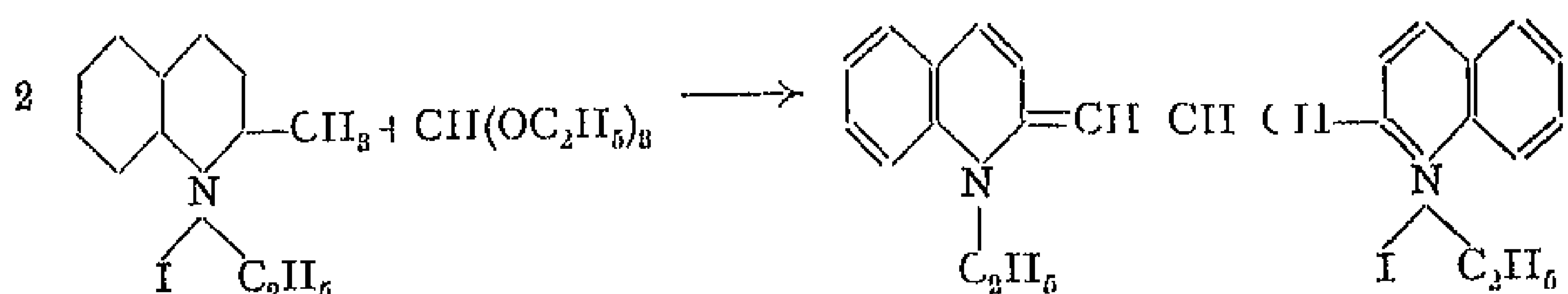
The sodium salt of quinaldine disulphonic acid is the dye-stuff **quinoline yellow**. This dyes a very pure and fast yellow, but owing to the high price its use is limited.

Lepidine, 4-*methyl-quinoline*, b.p. 257°, is also present in coal tar and was isolated by Williams from the product obtained on distilling cinchonine with caustic potash. **6-Methoxy-lepidine**, m.p. 50° to 52°, was obtained from quinine by treatment with potassium hydroxide (Konigs), and is formed synthetically by the condensation of *p*-anisidine with acetone and methylal.[3]

When a mixture of the iodo-alkyl derivatives of quinoline and quinaldine (or lepidine) is treated with alkali, there are formed **cyanines**,[1] strongly basic substances which dye a blue colour. Owing

[1] Kaufmann and Hüssy, *Ber.*, 1908, 41, 1735. [2] Besthorn and Geisselbrecht, *Ber.*, 1920, 53, 1017. [3] A. Pictet and Misner, *Ber.*, 1912, 45, 1800. [1] For the constitution of these, see Miethe and Book, *Ber.*, 1904, 37, 2008, 2821; A. Konig, *J. pr. Ch.* (2), 1906, 73, 100; Vongerichten and Hofchen, *Ber.*, 1908, 41, 3054; Mills and Braunholtz, *J. C. S.*, 1923, 123, 2804.

to their sensitiveness towards acids and light they cannot be employed as dye-stuffs, but are nevertheless of great value in photochemistry, particularly in colour photography *Cyanine or carbocyanine dyes* are best prepared according to Hamer,[1] by condensing the quaternary salts containing reactive methyl groups with ethyl orthoformate in the presence of pyridine The reaction may be illustrated by the preparation of **pinacyanol**, 1 1′-*diethyl* 2 2′-*carbocyanine halide*, from quinaldine ethiodide



Quinaldine ethiodide Pinacyanol

Pinacyanol is one of the most important photographic sensitisers

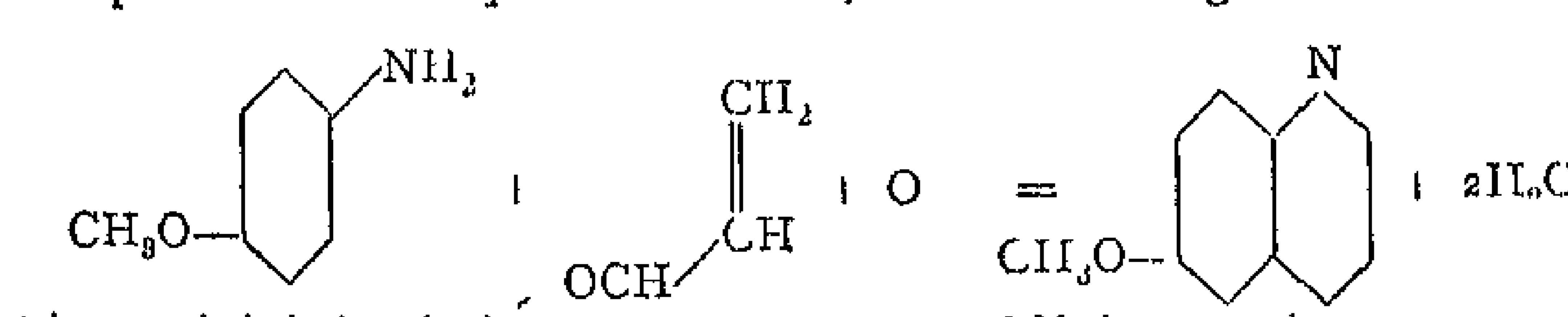
Flavaniline, 2-*aminophenyl*-4-*methyl-quinoline*, may be produced by heating acetanilide with zinc chloride, or by the condensation of equimolecular proportions of *o*- and *p*-amino-acetophenones Its monacid salts are beautiful yellow dyes, which dye wool and silk pure shades of yellow

Hydroxy quinolines

The hydroxy derivatives of quinoline possess the basic character of quinoline as well as the acidic character of phenol

Among compounds containing the hydroxy group attached to the benzene nucleus, **loretine**, 7-*iodo*-8-*hydroxy-quinoline*-5-*sulphonic acid*, $C_6HI(OH)(SO_3H)\ C_3H_3N$, is used as a substitute for iodoform

The *methyl ether of* 6-*hydroxy quinoline* has been known for a considerable time, and was first obtained by fusing the alkaloid quinine with caustic potash It may be prepared synthetically by Skraup's method from *p*-amino-anisole, in the following manner —

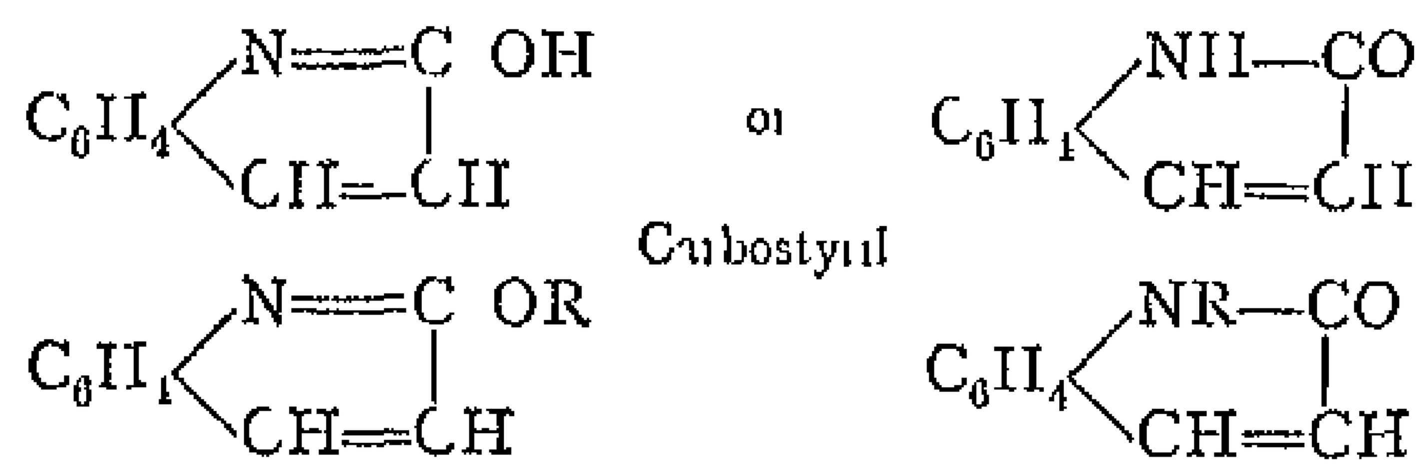


p Amino-anisole (*p* Anisidine) 6 Methoxy quinoline

Hydroxy-quinolines containing the hydroxyl group in the 2- or 4-position of the pyridine nucleus exhibit the same peculiar tautomerism as the hydroxy-pyridines (see p 642) They react in the hydroxylic form as true hydroxy quinolines, and also in the ketonic form as quinolones It has not yet been decided which structure represents

[1] Miss F M Hamer, *J C S*, 1927, 2696, 1928, 1472

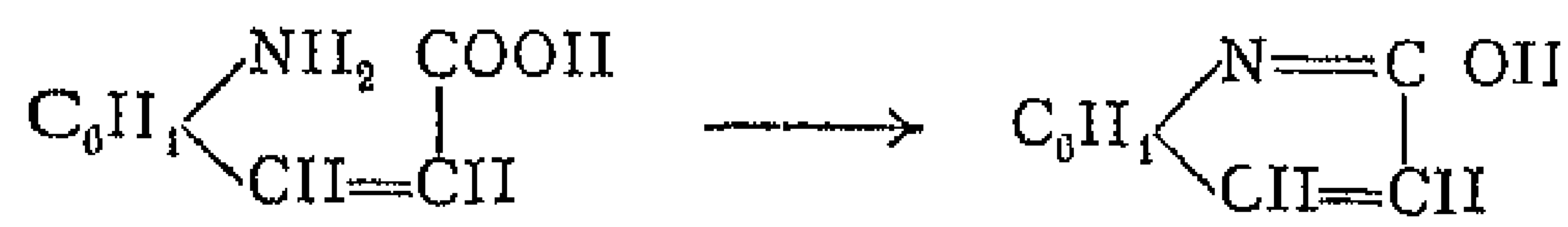
the free compounds On the other hand, the ethers exist in both modifications



Carbostyril

2 Alkoxy quinolines 1 Alkyl 2 quinolones

Carbostyril, *2-hydroxy-quinoline*, is obtained synthetically by the methods described on p 651, *e g* by the reduction of *o*-nitro-cinnamic acid, or by heating *o*-amino-cinnamic acid[1] (prepared from the *o*-chloro-acid) Hence it is to be regarded as an inner anhydride (lactam or lactim) of *o*-amino-cinnamic acid



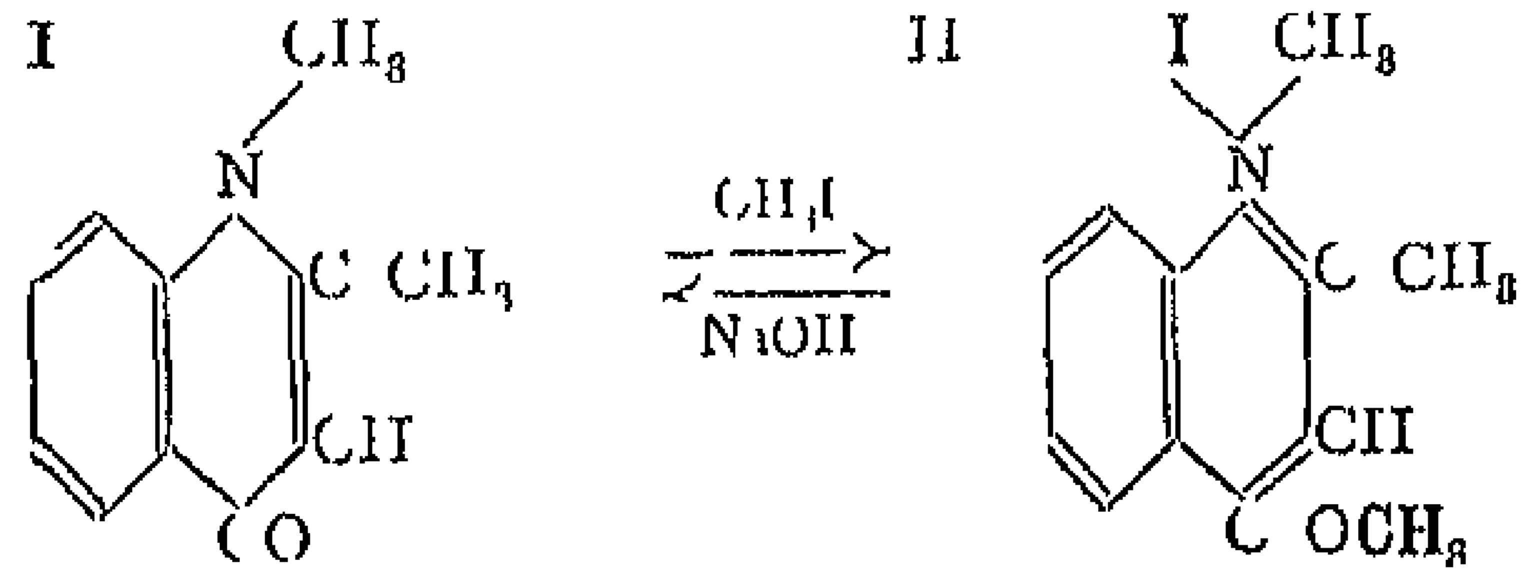
o Amino cinnamic acid Carbostyril

It can be prepared from quinoline by warming with a solution of bleaching powder It crystallises with 1 mol H_2O, and when anhydrous melts at 201° With acids and alkalis it forms salts which are decomposed by water

Kynurine, *4-hydroxy-quinoline*, is formed by heating kynurenic acid (see p 593), or by the oxidation of cinchonine It melts at 201°, and on treatment with phosphorus pentachloride yields 4-chloro-quinoline

4-Quinaldone, *4-hydroxy-2-methyl quinoline*, is obtained from the anil of acetoacetic ester (see pp 652), and gives two isomeric methyl ethers, *4-methoxy-quinaldine*, b p 298°, and *1-methyl-4 quinaldone* (I) It is worthy of emphasis that these two ethers yield one and the same methiodide with methyl iodide The first compound adds the alkyl halide normally to the nitrogen atom, the second, on the other hand, unites with methyl iodide by 1 5-addition, in the same manner as antipyrine (see p 618 *et seq*), to form the methiodide of 4-methoxy-quinaldine (II) This methiodide shows a great resemblance to the *pseudo*-methiodide of antipyrine, and is easily converted into the original methyl-quinaldone by fusion or treatment with aqueous alkali[2]

I II



[1] H Meyer and Beer, *Monats*, 1913, 34, 1173
[2] L Knorr, *Ber*, 1897, 30, 922, 927
Ann, 1903, 328, 81

In this way it is therefore possible to convert 4-methoxy-quinaldine into 1-methyl-4-quinaldone. The rearrangement of bonds which occurs during the change is similar to that accompanying the isomerisation of the desmotropic forms of a tautomeric substance.

Benzoyl chloride also combines with methyl quinaldone in the same manner as methyl iodide. The addition product is decomposed into its components instantaneously by aqueous alkali, and gradually by the action of cold water or boiling alcohol.

Quinolyl Ketones

Quinoline-8-aldehyde, which strongly resembles benzaldehyde in properties, reacts with organo-magnesium halides to form *8-quinolyl-carbinols*. These, on oxidation with potassium bichromate and sulphuric acid, pass into the corresponding *8-quinolyl ketones*.[1]

A productive method of preparing *4-quinolyl-ketones* lies in the action of organo-magnesium halides on esters and nitriles of quinoline-carboxylic acids,[2] *e.g.* 4-quinoline-carboxylic esters on treatment with ethyl magnesium iodide yield, among other products, *4-quinolyl-ethyl-ketone*.

$$NC_9H_6 \cdot COOR \longrightarrow NC_9H_6 \cdot CO \cdot C_2H_5$$

The 4-quinolyl-ketones bear a distant structural resemblance to the *cinchona toxines*, which are degradation products of the cinchona alkaloids. They may be converted into amino-alcohols which are related to these alkaloids.

Quinoline Carboxylic Acids

All of the carboxylic acids corresponding to the seven methyl quinolines are known. Those containing the carboxyl group in the benzene ring may be prepared from amino-benzoic acids by Skraup's synthesis.

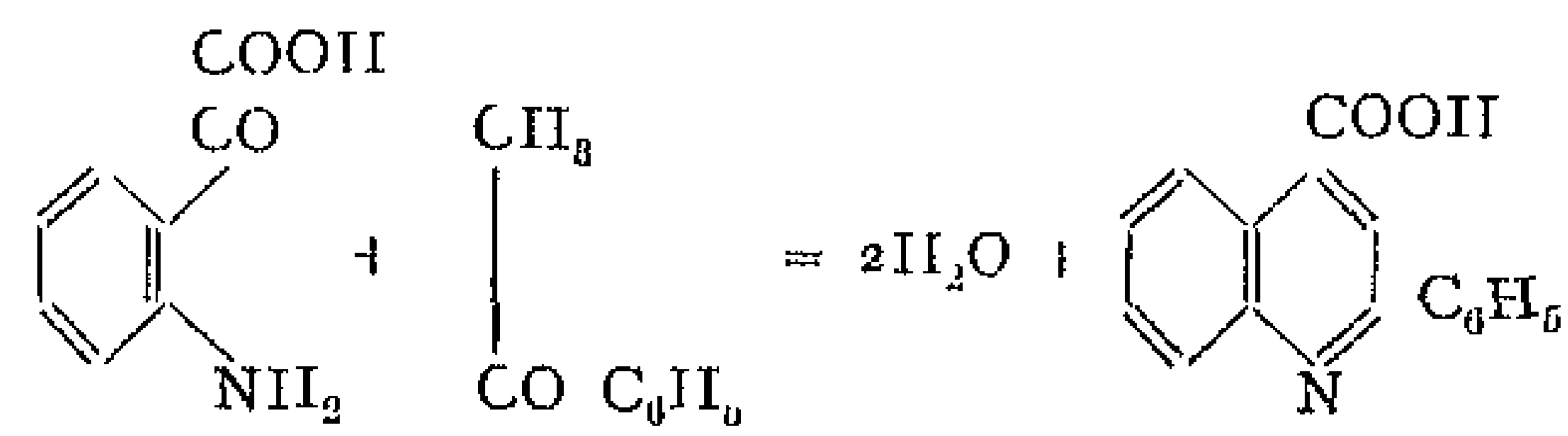
Among quinoline carboxylic acids containing the carboxyl group in the pyridine ring, the following may be mentioned:—

Quinoline-2-carboxylic acid, **quinaldinic acid**, results from the oxidation of quinaldine with chromic acid. The hydrated acid ($2H_2O$) melts at 156°. A convenient method of preparing quinaldinic acid in good yield consists in heating quinaldine with formaldehyde, and oxidising the methylol-compound so obtained with nitric acid.[3]

Quinoline-4-carboxylic acid, **cinchoninic acid**, has been isolated from the products obtained on oxidising the alkaloid cinchonine with potassium permanganate, nitric acid or chromic acid, and is also formed by the oxidation of other cinchona alkaloids. It melts at 254°.

[1] Howitz and Köpke, *Ann.*, 1913, 396, 38.
[2] A. Kaufmann and co-workers, *Ber.*, 1913, 46, 57; Rabe and Pasternack, *ibid.*, 1026.
[3] Königs, *Ber.*, 1899, 32, 223; Besthorn and Ibele, *Ber.*, 1906, 39, 2329.

α-Phenyl-quinoline-γ-carboxylic acid, **atophane**, is used as a remedy in arthritic diseases owing to its power of removing uric acid from the system It is obtained from isatic acid and acetophenone



The examination of a large number of atophane derivatives[1] shows that the structure requisite for the above physiological action is a quinoline nucleus with an aryl group in position 2 and a carboxyl in position 3 or 4

6-Methoxy-quinoline-4 carboxylic acid, **quininic acid**,[2] is a methoxy-derivative of cinchoninic acid It was obtained by Skraup by oxidising the alkaloid quinine with chromic acid The constitution of quininic acid is shown by its conversion into pyridine-2 3 4-tricarboxylic acid on oxidation with potassium permanganate, and by the formation of 6-hydroxy-quinoline when it is treated with hydrochloric acid and distilled It is produced synthetically by condensing *p*-anisidine with methylal and pyroracemic ester, and hydrolysing the ester so formed[3] It crystallises in prisms, which melt at 280° with decomposition

4-Hydroxy-quinoline-3-carboxylic acid, **kynurenic acid**, occurs in the urine of dogs, in which, as has been shown by Ellinger, it originates from tryptophane (p 593) It does not appear to be formed in the human system The constitution of the acid has been confirmed by synthesis[4]

Hydroquinolines

Hydrogen readily adds on to quinoline and its derivatives Treatment with zinc and hydrochloric acid, or sodium and alcohol, leads to four atoms of hydrogen being taken up by the pyridine nucleus with the formation of *tetrahydro-quinolines* These possess the properties of secondary fatty-aromatic amines

1 2-**Dihydro-quinoline**, $C_6H_4\left\langle\begin{matrix} CH & CH \\ NH & CH_2 \end{matrix}\right.$, b p 226°, is obtained synthetically[5] by heating *o*-toluidine with chloro- or bromo-acetal in a

[1] J v Braun and I Bruns, *Ber*, 1927, 60, 1253 [2] This compound is very often referred to as quinic acid The name quininic acid, however, emphasises the relationship to cinchoninic acid and avoids confusion with tetrahydroxy-hexahydro benzoic acid, which is found associated with quinine in nature and is also known as quinic acid (see p 463) [3] A Pictet and Misner, *Ber*, 1912, 45, 1800 Compare also A Kaufmann, *Ber*, 1922, 55, 614 [4] E Späth, *Monats*, 1921, 42, 89 [5] C Rath, *Ber*, 1924, 57, 550

sealed tube to temperatures above 200°. It is a colourless liquid which gradually turns yellow in air.

Tetrahydro quinoline, $C_6H_4\left<\begin{array}{l}NH-CH_2\\ \qquad\quad |\\ CH_2-CH_2\end{array}\right.$, b.p. 245°, is a liquid at ordinary temperatures. Oxidising agents convert it into quinoline. In its general behaviour it shows a great resemblance to methylaniline. As indicated on p. 634, tetrahydro-quinoline may be transformed by various intermediate stages into *chromane*. This series of reactions represents the replacement of the imino-group of tetra-hydro-quinoline by an oxygen atom.

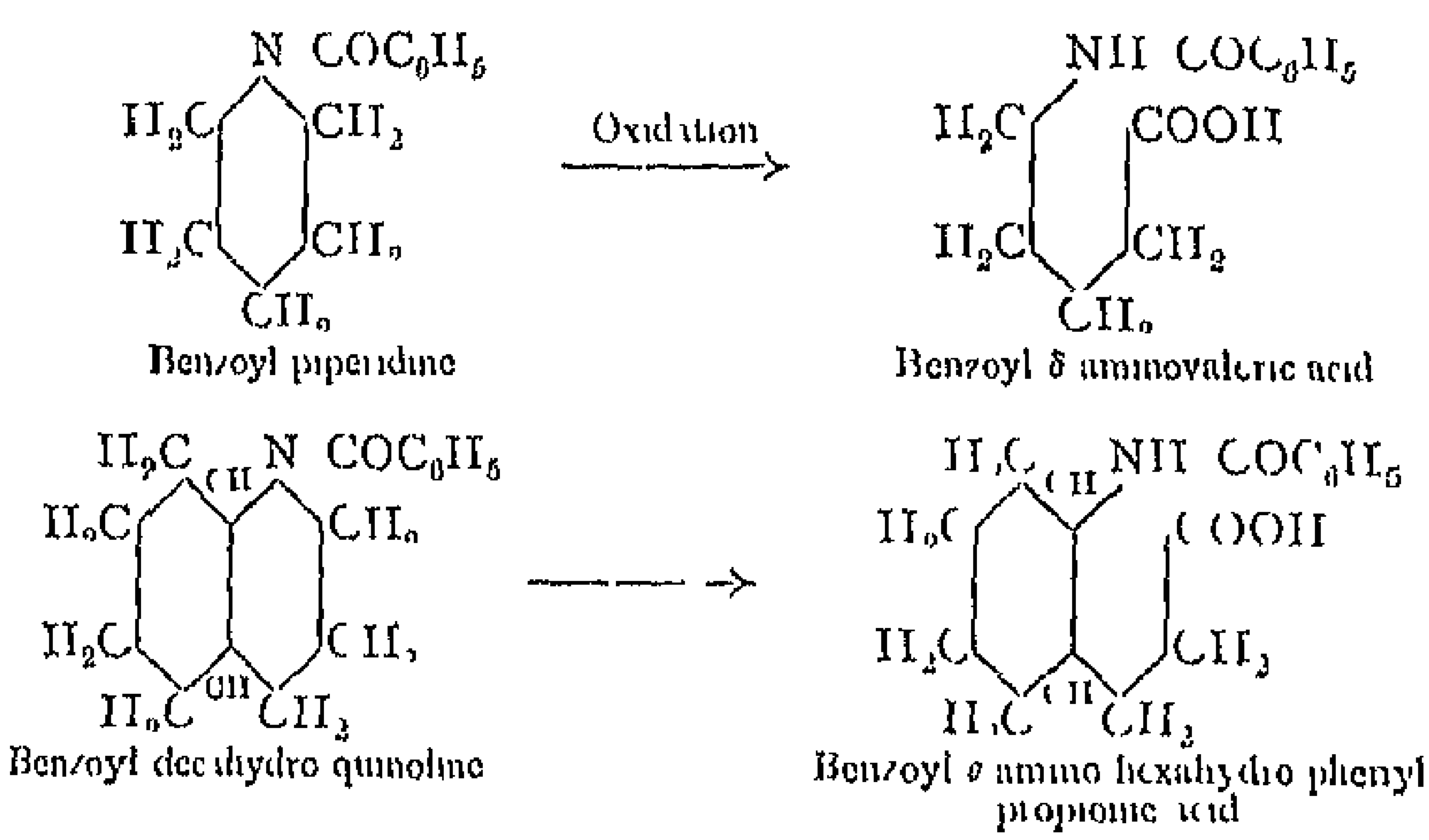
8-*Hydroxy-1-methyl-tetrahydro-quinoline*, $C_9H_9(OH)N\cdot CH_3$, **kairine**, and 6-*methoxy-tetrahydro quinoline*, $C_9H_9(OCH_3)NH$, **thalline**, have been employed medicinally as febrifuges in the form of their salts.

Under the influence of very energetic reducing agents, such as hydriodic acid and phosphorus at high temperatures, quinoline or the tetrahydro compound can be converted into **hexahydro quinoline** (b.p. 226° under 720 mm.) and finally **decahydro quinoline**

$$\begin{array}{l}CH_2-CH_2-CH-NH-CH_2\\ |\qquad\qquad\quad\ |\qquad\qquad\qquad |\\ CH_2-CH_2-CH-CH_2-CH_2\end{array}$$

The latter crystallises in needles, m.p. 48.5°, and boils at 204°. It is a strong secondary base, and in its chemical nature may be regarded as the piperidine of the quinoline group.

Thus, for example, its benzoyl derivative on oxidation undergoes fission in exactly the same way as benzoyl-piperidine.



Benzoyl piperidine → Benzoyl δ aminovaleric acid

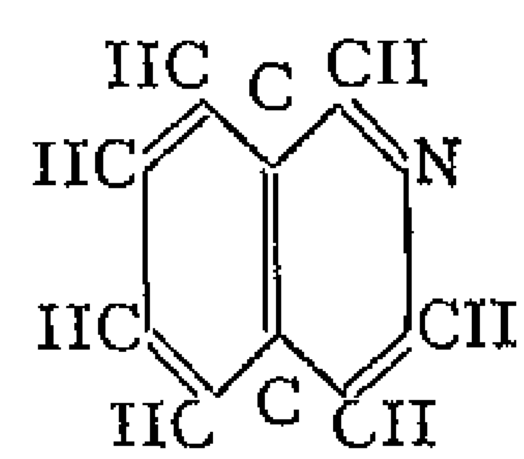
Benzoyl decahydro quinoline → Benzoyl o amino hexahydro phenyl propionic acid

as the pyridine ring can be fused with a benzene nucleus to give quinoline, also be condensed with naphthalene, anthracene, and other nuclei, by

making use of naphthylamines, anthramines, etc, in the Skraup synthesis In this manner there are formed *condensed quinolines*, such as α and β naphthoquinoline, anthraquinoline, and so on

ISOQUINOLINE

Isoquinoline, like quinoline, represents the fusion of a pyridine ring with a benzene ring In this case, however, the union is not in the $\alpha\beta$- but in the $\beta\gamma$-position of the pyridine nucleus, as will be seen from the following formula

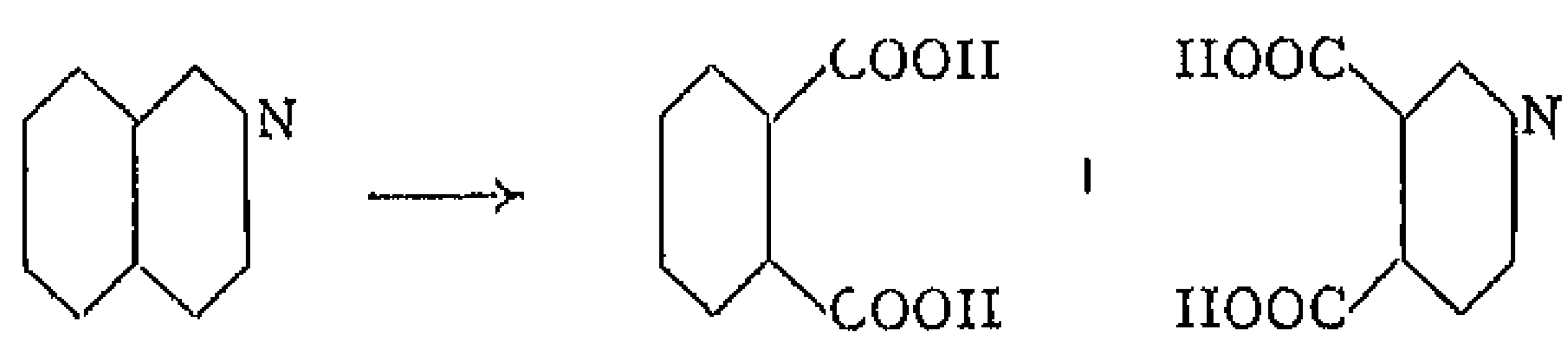


Isoquinoline

Isoquinoline may therefore be considered as naphthalene in which one of the CH-groups in the β-position has been replaced by a nitrogen atom

This constitution has been confirmed by the degradation of isoquinoline and its derivatives, as well as by synthesis

By the *oxidation of isoquinoline* with potassium permanganate the benzene ring and the pyridine ring are both attacked, and a mixture of phthalic acid and cinchomeronic acid is obtained

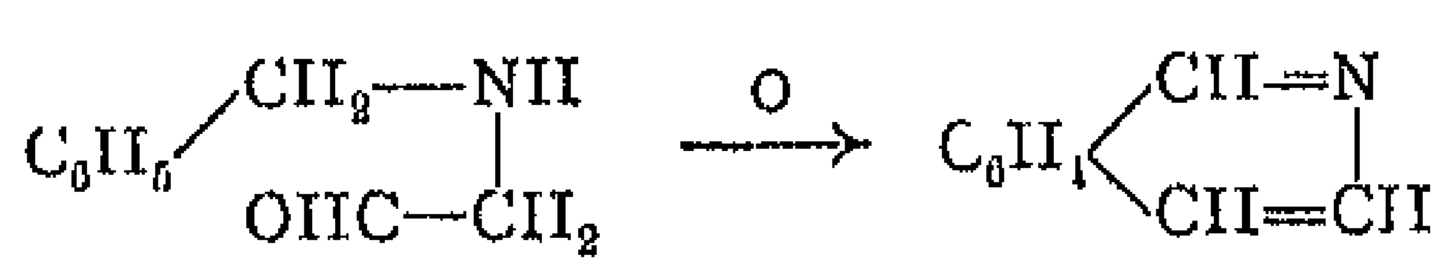


Isoquinoline Phthalic acid Cinchomeronic acid

Among *syntheses* proving the structure of isoquinoline and its derivatives, the following may be mentioned

1 Benzylamino-acetaldehyde (I), and also benzylidene-amino-acetal, $C_6H_5CH:N\cdot CH_2\cdot CH(OC_2H_5)_2$, readily pass into isoquinoline under the influence of fuming sulphuric acid

I



2 A useful synthetic method of preparing isoquinoline, which starts from homophthalic acid, is due to Gabriel (1886) Ammonium homophthalate on distillation yields *homophthalimide* (II), this when

heated with phosphorus oxychloride is converted into *dichloro-isoquinoline* (III), from which by reduction with hydriodic acid and phosphorus is obtained isoquinoline

$$\overset{\text{II}}{C_6H_4\begin{cases}CO-NH\\ CH_2-CO\end{cases}} \longrightarrow \overset{\text{III}}{C_6H_4\begin{cases}CCl=N\\ CH=CCl\end{cases}} \longrightarrow C_6H_4\begin{cases}CH=N\\ CH=CH\end{cases}$$

3 Isoquinoline may also be produced by passing the vapour of benzylidene-ethyl-amine through a tube heated to redness[1]

$$C_6H_4\begin{cases}CH=N\\ CH_2-CH_2\end{cases} \longrightarrow C_6H_4\begin{cases}CH-N\\ CH-CH\end{cases} + 4H$$

4 Acyl derivatives of ω phenyl-ethylamine can be condensed to derivatives of dihydro-isoquinoline, *e g* by use of phosphorus pentachloride or oxychloride[2]

$$C_6H_5\begin{cases}R\ CO-NH\\ CH_2-CH_2\end{cases} \longrightarrow C_6H_4\begin{cases}CR-N\\ CH_2-CH_2\end{cases} + H_2O$$

Of the numerous syntheses effected in this way, one of the most important is that of hydrastinine (see later) This synthesis also throws some light on the origin of isoquinoline complexes in plants

5 An interesting synthesis of isoquinoline is by anhydride formation from cinnamic aldoxime, on warming with P_2O_5 This reaction is probably analogous to the Beckmann transformation, the phenyl-vinyl group (C_6H_5 CH CH) and the hydroxyl radical first changing places, and water subsequently being liberated[3]

$$\begin{matrix}C_6H_5\ CH\ CH\ CH\\ \|\\ HO-\!\!-\!\!-\!\!-N\end{matrix} \longrightarrow \begin{matrix}HO-\!\!-\!\!-\ CH\\ \|\\ C_6H_5\ CH\ CH\ N\end{matrix} \longrightarrow \begin{matrix}C_6H_4\quad CH\\ |\qquad\ \|\\ CH\ CH\ N\end{matrix} + H_2O$$

Isoquinoline is found in small amounts with quinoline in coal tar, and can be separated from the latter by taking advantage of the low solubility of its sulphate It is a colourless liquid, m p 23° and b p 240°, which in smell and other properties strongly resembles quinoline

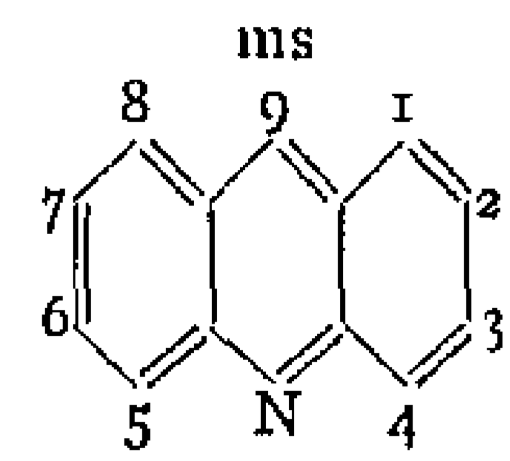
It is of importance on account of the fact that certain well-known vegetable alkaloids, such as papaverine, laudanosine, narcotine and hydrastine, are derived from it In the description of these substances given later, a number of isoquinoline derivatives obtained from them by degradation will also be met with

[1] Pictet and Popovici, *Ber*, 1892, 25, 733 [2] A Pictet and Kay, *Ber*, 1909, 42, 1973 Pictet and Spengler, *Ber*, 1911, 44, 2030 H Decker and co workers, *Ann*, 1913, 395, 299
[3] Bamberger and Goldschmidt, *Ber*, 1894, 27, 1954, 2795

Acridine Group

Acridine is a dibenzo-pyridine, and stands to quinoline in the same relationship as anthracene to naphthalene. It may be regarded as anthracene in which one of the central CH groups is replaced by N.[1]

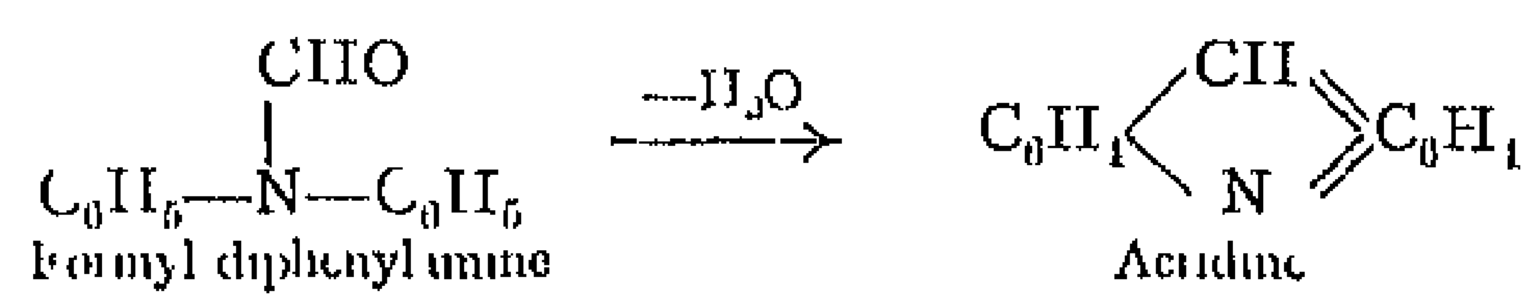
Acridine occurs in the crude anthracene of coal tar, and is the parent substance of various dyestuffs of industrial value. It crystallises in colourless needles, which sublime easily and melt at 110°. In solution it has a blue fluorescence, a property peculiar to all the acridine bases. This fluorescence is particularly pronounced in ethereal solution.



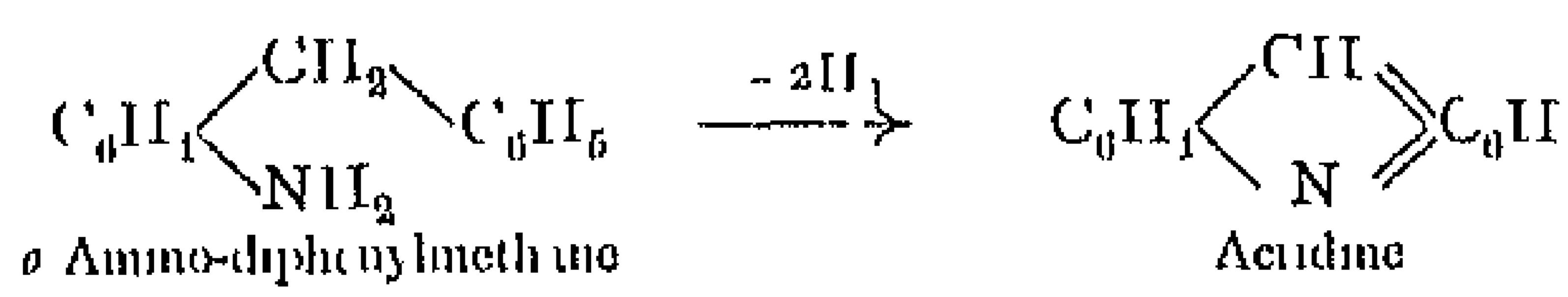
The acridines are weaker bases than the pyridines or quinolines, and are marked by their great stability.

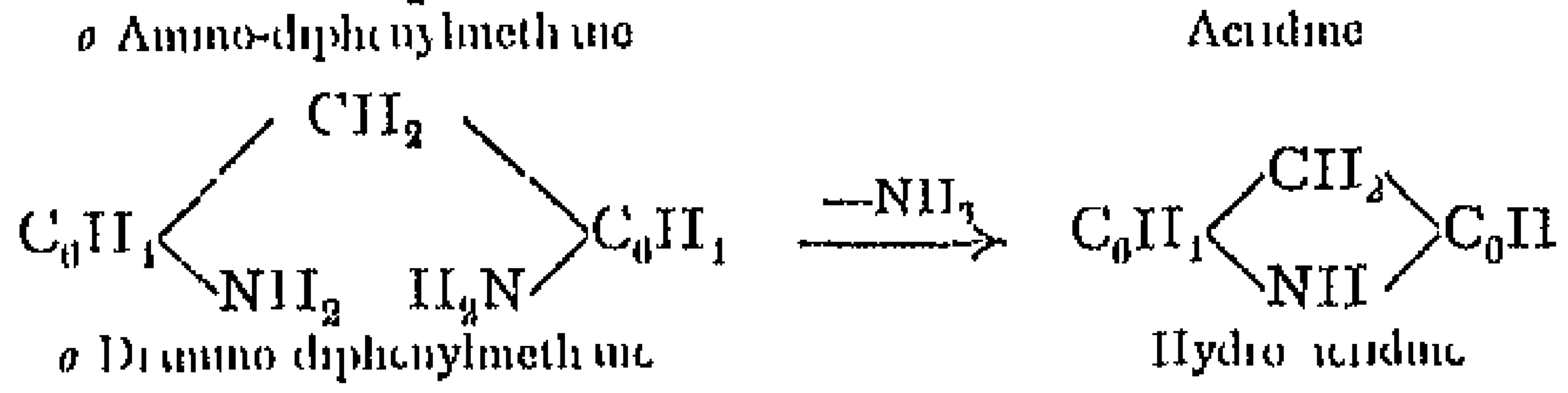
They are formed synthetically by various methods, *e.g.*

1. By the action of zinc chloride on acyl derivatives of diphenylamine. Thus formyl-diphenylamine, on heating with zinc chloride, yields acridine (Bernthsen).



2. *o*-Amino-diphenylmethane is converted into acridine on oxidation;[2] and ammonia can be eliminated from *o*-diamino-diphenylmethane and *o*-diamino-triphenylmethane with the formation of *hydro acridines*. Tetra-amino-diphenyl-methane yields 3 6 *diamino-acridine*.[3] *o*-Nitro-diphenylmethane at high temperature (300°) passes into 9-*acridone*.[4]



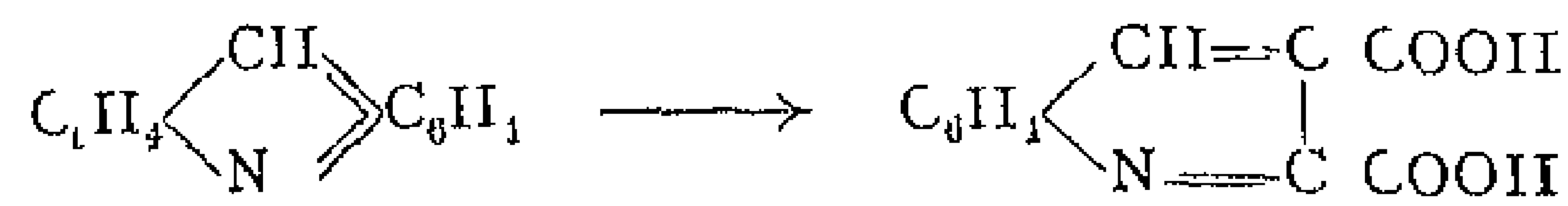


Tetrahydro acridines result from the condensation of aromatic *o*-amino-aldehydes (or *o*-amino-ketones) with hydroaromatic ketones[5] containing the group CH_2CO.

The constitution of acridine follows from these syntheses, and is further confirmed by the formation of quinoline-2 3-dicarboxylic acid,

[1] For constitution, see K. v. Auwers and R. Kraul, *Ber.*, 1925, 58, 543. [2] O. Fischer and Schütte, *Ber.*, 1893, 26, 3083. For *syntheses of naphthacridines*, *cf.* F. Ullmann and co-workers, *Ber.*, 1900, 33, 905; 1903, 36, 1027; 37, 2922; 39, 298, 356. For the formation of *derivatives of 10-phenyl acridine*, see F. Mayer and Freund, *Ber.*, 1922, 55, 2049. [3] J. Benda, *Ber.*, 1912, 45, 1787. [4] A. Kliegl, *Ber.*, 1909, 42, 591. [5] Borsche and co-workers, *Ber.*, 1908, 41, 2203.

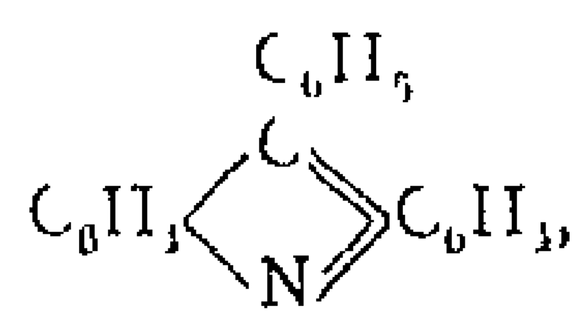
known as *acridinic acid*, when acridine is oxidised with potassium permanganate



By the entrance of amino groups (auxochromes) into the acridine molecule it acquires the properties of a dye, the pyridine ring functioning as the chromophoric group. The resulting dye-stuffs generally contain the amino-groups in positions 3 and 6.

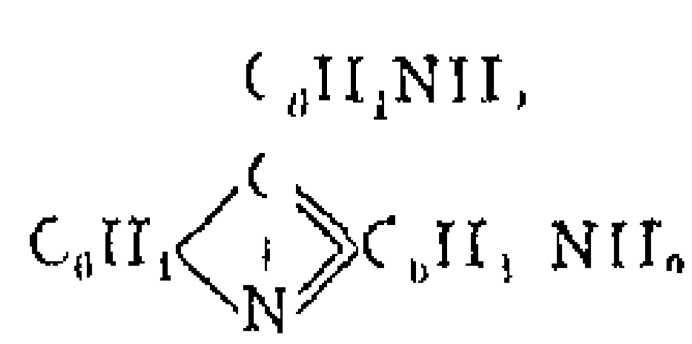
6 9-*Diamino-acridine* and its substitution products are therapeutically active against streptococci. The highest activity in this sense is shown by 2-ethoxy-6 9-diamino-acridine, the hydrochloride of which is employed under the name of "*Rivanol*".[1]

Acridine yellow, 2 7-*dimethyl*-3 6-*diamino-acridine*, is prepared by condensing *m*-tolylene-diamine with formaldehyde, whereby tetramino ditolylmethane is first produced. On being heated with hydrochloric acid, this loses ammonia and forms 2 7-dimethyl-3 6-diamino-hydroacridine (see above), which on oxidation yields the dye-stuff. Acridine yellow gives beautiful fluorescent colourings, particularly on silk, but these are not very fast to light.

From *phenylacridine*,  are derived the benzoflavines and chrysanilines.

Benzoflavine, 3 6 *diamino phenylacridine*, is obtained in a similar manner to acridine yellow by the condensation of benzaldehyde (in place of formaldehyde) with *m*-phenylene diamine. The commercial product appears to be prepared from *m*-tolylene diamine and, with the aid of tannin, dyes cotton, wool and silk a fine yellow colour.

Chrysaniline, ms-*p aminophenyl-2-amino-acridine*,



is formed as a by-product in the preparation of fuchsine. Its constitution has been established by O. Fischer and Körner, by synthetic and analytical methods. For example, on diazotisation and boiling with alcohol it gives *ms*-phenylacridine. It may be synthesised by the condensation of *o*-nitrobenzaldehyde with aniline to form *o*-nitro *p* diamino-triphenylmethane, the latter can then be reduced to the triamino compound, which yields chrysaniline on oxidation. The

[1] For other compounds, see *J. C. S.*, 1922, **122**, Abs. i, 468

crude nitrate or hydrochloride is placed on the market under the name of "**Phosphine**." It dyes wool and silk directly and cotton with the aid of tannin mordant, giving an orange-tinted yellow colour. It is chiefly used for silk.

VII

The Vegetable Alkaloids[1]

Introduction

The alkaloids are now generally defined as basic compounds of vegetable origin, in which at least one nitrogen atom forms part of a cyclic system. This definition, however, does not include certain members of the group. Many of these compounds possess curative properties and are of great value in medicine.

Although the poisonous and therapeutic properties of various plants have been known and utilised from early times, it was not until 1817 that the first alkaloid was isolated. A large number of these compounds are now known, but for a long time all attempts to determine their constitutions or to prepare them synthetically were fruitless.

The chemistry of the alkaloids began to make definite progress with the discovery of pyridine and quinoline, which led to the view that they were related to these bases in the same manner as aromatic compounds to benzene. Königs, in 1880, defined alkaloids as naturally occurring organic bases, which are derived from pyridine.

This suggestion proved of great value in promoting our knowledge of the chemistry of pyridine, but did not hold true for all alkaloids. Later, the systematic classification of the alkaloids as derivatives of pyridine, or indeed as belonging to any single class of organic compound, had to be abandoned, owing to the discovery that natural groups of vegetable bases, such as the morphine and coca groups, cannot be referred to any one parent substance but belong to a number of different systems.

In describing all the vegetable bases as alkaloids, we are therefore collecting into one class a number of substances of widely differing constitutions. A few of these contain nitrogen in an open chain, but in general it is present in a cyclic structure such as that of pyridine, quinoline, isoquinoline or pyrrole. Still other alkaloids are derived from purine, or from complex dicyclic systems such as are contained in the "second half" of the cinchona alkaloids and in the tropine group.

[1] See T. A. Henry, *The Plant Alkaloids* (Churchill, 1924). J. Schmidt, *Über die Erforschung der Konstitution und die Versuche zur Synthese wichtiger Pflanzenalkaloide* (Enke, 1900). *Handbuch der biologischen Arbeitsmethoden*, edited by E. Abderhalden (Berlin, 1920). J. Schwyzer, *Die Fabrikation der Alkaloide* (Springer, 1927). E. Späth, "Neuere Ergebnisse der Alkaloidchemie," *Zeitsch. f. ang. Ch.*, 1928, 41, 1231, 1257.

Preparation of Alkaloids from Plants and their General Properties[1]

Alkaloids are usually found in plants in the form of salts—in which they are either united to the common plant acids (*e.g.* malic or citric acid) or to certain characteristic acids such as quinic acid, in the cinchona alkaloids, and meconic acid, in those of the opium group. Their distribution is very unequal. Although they may be detected in all parts of the plant, they generally accumulate in the fruit and seeds, and also in the bark of trees.[2]

In the preparation of alkaloids from plants, the finely divided material is usually extracted with water containing hydrochloric or sulphuric acid. This liberates the alkaloids from their salts with organic acids, and the bases pass into solution as hydrochlorides or sulphates, together with dye-stuffs, carbohydrates and other products from the plant tissue. From the solution so obtained the alkaloids, being insoluble or only sparingly soluble in water, can be precipitated by the addition of alkali. If the bases are volatile, as in the case of nicotine, the solution or finely-divided raw material is treated with alkali and distilled in steam. The crude alkaloids are then purified by special methods, frequently by recrystallisation of the free compounds or their salts.

The majority of the alkaloids are solid substances which cannot be distilled; only a few, such as coniine, are liquid and volatilise without decomposition. On the animal organism, as has already been mentioned, they often exert a marked physiological action. Almost without exception they are either insoluble or sparingly soluble in water, dissolve with more or less difficulty in chloroform, ether and benzene, and readily in alcohol. Most of the alkaloids are optically active and usually laevorotatory. In many cases their solutions give a strong alkaline reaction.

All of them form salts with acids, among which the hydrochlorides, sulphates and oxalates crystallise particularly well. Like the salts of other bases, they possess the property of uniting with certain metallic salts such as the chlorides of mercury, platinum and gold, to form double compounds.

Alkaloids are precipitated from aqueous or acid solution by a number of substances generally known as *alkaloid reagents*, *e.g.* tannic acid, picric acid, picrolonic acid, perchloric acid, potassium mercuric iodide, potassium bismuth iodide, phosphomolybdic acid and phosphotungstic acid. These reagents, however, are of no great value for the quantitative analysis of alkaloids, since the resulting compounds are not sufficiently insoluble and because the reagents also precipitate other organic substances.

[1] See also Henry, *loc. cit.* [2] On the mode of formation of alkaloids in plants, see Pictet, *Ber.*, 1907, **40**, 3771. Robinson, "A Theory of the Mechanism of the Phytochemical Synthesis of Certain Alkaloids," *J. C. S.*, 1917, **111**, 876; R. C. Menzies and R. Robinson, *J. C. S.*, 1924, 2163.

Methods of Determining the Chemical Constitution of Alkaloids

In attempting to determine the structure of an alkaloid, one of the first tasks is to investigate the action of *hydrolysing agents* When heated with water, acids or alkalis, many of the vegetable bases break up into a characteristic alkaloidal constituent, containing nitrogen, and a nitrogen-free component In general, the latter consists of an acid, the carboxyl group of which was originally combined with the basic group or with an alcoholic hydroxyl of the nitrogenous constituent, in the comparatively rare gluco-alkaloids, among which is numbered solanine, the second component is a sugar

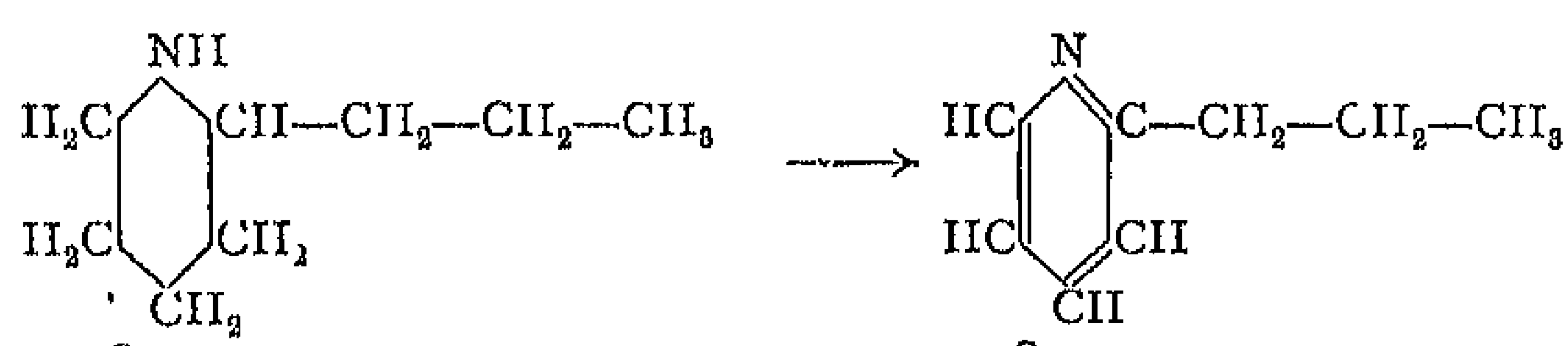
Thus piperine decomposes on hydrolysis into piperidine and piperic acid, the union in this case is of the acid-amide type

$$\begin{array}{l}(C_5H_{10})N\text{—}CO\text{—}C_{11}H_9O_2\\ \qquad\quad\;\; H \quad\; OH\end{array}$$

Atropine, as will be seen later, may be hydrolysed to give tropic acid and the alkamine tropine

A second method is to effect a *degradation by distillation with zinc dust*, *fusion with alkali*, or *heating with bromine* or other vigorous reagents, as a result of which some stable parent substance can often be isolated

Gerhardt, as early as 1842, obtained quinoline from cinchonine by distilling the latter with alkali Vongerichten and Schrotter isolated phenanthrene as the main product of the distillation of morphine with zinc dust Alkaloids containing oxygen generally lose this element on treatment with zinc dust, while those rich in hydrogen become dehydrogenised Our knowledge of the constitution of coniine, for example, is based on Hofmann's observation that on distilling the compound with zinc dust it loses six hydrogen atoms to give conyrine (2 propyl-pyridine)



Coniine Conyrine

Other methods of removing hydrogen have already been quoted under piperidine (see p 646) Meroquinene has been shown to be a pyridine derivative by Konigs, who obtained 3-ethyl-4-methyl-pyridine by heating it with hydrochloric acid and mercuric chloride

In the *hydrogenation of alkaloids*, an important part is played by *catalytic methods of reduction*, involving the use of metals of the

platinum group In this manner morphine readily yields dihydro-morphine, and the cinchona alkaloids give dihydro-derivatives

In addition, the *estimation of the methylimino-group*, as developed by Herzig and Meyer,[1] is being employed more and more in alkaloid investigation When the hydriodides of N-methylated bases are heated at 200° to 300°, they part with methyl iodide according to the equation

$$R \cdot N\begin{cases} CH_3 \\ H \\ I \end{cases} = R \cdot NH + CH_3I$$

The methyl iodide can be estimated by Zeisel's method, in which it is absorbed in an alcoholic silver nitrate solution and the resulting silver iodide weighed

Zeisel's method for the determination of methoxyl groups depends on the conversion of the methyl of the CH_3O-group into methyl iodide, by treatment with hydriodic acid at the boiling-point, and the subsequent estimation of iodine in the above manner

A process for the *determination of methoxyl in the presence of methyl-imino groups* (Herzig and Meyer) is based on the fact that the methoxyl group is hydrolysed at the boiling point of hydriodic acid, whilst the N-methyl group is not detached until a higher temperature has been reached With regard to the value of this method for distinguishing between a methoxyl and a methylimino group, it appears that a negative result at the lower temperature may safely be taken to prove the absence of methoxyl, but otherwise no certain conclusion can be drawn without further information[2]

Fourthly, *the function of the oxygen atoms* in the alkaloid must be investigated In this connection a reaction of special importance is the conversion of an alkaloid containing an alcoholic hydroxyl group into its anhydro compound, by means of dehydrating agents such as a solution of glacial acetic acid in sulphuric acid (*e g* tropine --> tropidine)

$$\underset{\text{Tropine}}{(C_6H_{11}N)\begin{matrix} -CHOH \\ | \\ CH_2 \end{matrix}} \qquad \underset{\text{Tropidine}}{(C_6H_{11}N)\begin{matrix} -CH \\ \| \\ -CH \end{matrix}} + H_2O$$

or by successive treatment with phosphorus chlorides and alcoholic potash (*e g*, production of cinchene and quinene from cinchonine and quinine) The unsaturated compounds so obtained are often more reactive than the original alkaloids, and can with advantage be submitted to reactions involving further degradation

[1] J Herzig and H Meyer, *Monats*, 15, 613, 16, 599, 1897, 18, 379 *Cf* also M Busch, *Ber*, 1902, 35, 1565 H Decker, *Ber*, 1903, 36, 2895 [2] See M Busch, *Ber*, 1902, 35, 1565, G. Goldschmiedt, *Monats*, 1906, 27, 849, 1907, 28, 1163, A Kirpal, *Ber*, 1908, 41, 819

Alcoholic and phenolic hydroxyl groups are estimated in the usual manner by acetylation and benzoylation.

Finally, the determination of the structure of an alkaloid generally necessitates an *investigation of the oxidation products*. Towards oxidising agents alkaloids offer a number of points of attack, such as ethylene linkings, $>C{=}C<$, carbinol groups, $>C\langle{}^{H}_{OH}$, methylimino groups, $>N\cdot CH_3$, and others.

Among the reagents used for this purpose, the most important are potassium permanganate, chromic acid, nitric acid, and hydrogen peroxide. Permanganate is of particular value in attacking a double bond between carbon atoms, when two hydroxyl groups are first added (see p. 112). The resulting glycols are best further oxidised by means of chromic acid, which leads to the molecule being ruptured at the point originally occupied by the double bond.

Hydrogen peroxide brings about oxidation at the nitrogen atom and opens up the ring. In the case of saturated compounds of an aliphatic nature, permanganate has the peculiar property—often observed in the tropine series—of oxidising the methyl group away from nitrogen.

A good example of the use of oxidation methods will be described later in connection with nicotine.

An interesting method frequently employed in examining the structure of alkaloids is to study the degradation products they yield on *exhaustive methylation*, by which in its widest sense is understood the decomposition of substituted ammonium hydroxides under the influence of heat, or of quaternary ammonium salts when treated with alkalis. The reactions employed in the exhaustive methylation of alkaloids are well illustrated by the degradation of N-methyl piperidine to piperylene (see p. 648), a classical example discovered by A. W. Hofmann. Another simple example will be found under apomorphine, p. 725. In this manner the carbon framework of the alkaloid molecule is revealed in the form of unsaturated hydrocarbons.

This method of decomposition may be applied to alkaloids with all conceivable groupings in the molecule, and also, which is of special importance, to amino-acids obtained by the oxidation of alkaloids. The degradation products formed in this way include a great variety of unsaturated non-nitrogenous compounds, including hydrocarbons, ketones, aldehydes and carboxylic acids. For determining the structure of alkaloids this method is therefore of great service, since these unsaturated products of exhaustive methylation can often be converted by simple reactions, such as reduction, into compounds of known constitution.

Tropinic acid, for example, on exhaustive methylation gave a

diolefine-dicarboxylic acid of the formula $C_7H_8O_4$, and of unknown structure, on reduction with sodium amalgam this was transformed into pimelic acid, a normal dicarboxylic acid containing seven carbon atoms (see p 272)

Hence it follows that the carbon skeleton in tropine and ecgonine must possess an unbranched chain of seven atoms, and that these are arranged in the form of a ring, since tropinic acid is produced from tropine and ecgonine by rupture of part of the cyclic system The application of the same principle also enabled this cycloheptane ring to be isolated intact from cocaine and atropine, in the form of its ketone, suberone

The value of exhaustive methylation, followed by reduction of the resulting degradation products, is not confined to the information this gives concerning structure, as it is often possible to effect a synthesis of the alkaloid by applying the method in the reverse direction

The *fission of cyclic bases by means of phosphorus halides* (J v Braun) has also been applied to the determination of alkaloid structure This treatment yields open chain halogen compounds (see p 647)

Information as to the effect of high temperature on an alkaloid can sometimes be gained by *fusion with urea* The behaviour of berberine, narcotine and hydrastine has been examined under these conditions [1]

Classification of the Alkaloids — In the succeeding pages the alkaloids are classified according to their chemical constitution, especially with reference to the basic compounds from which they are derived In most cases it is then found that alkaloids produced by one and the same plant, and therefore belonging to the same botanical group, also fall into the same chemical group, owing to the fact that the compounds generated by a given plant frequently possess similar chemical constitutions

The alkaloids are therefore divided into the following groups:

1 Hydroxy-phenyl alkylamine and phenyl hydroxy-alkylamine bases
2 Alkaloids of the pyridine group
3 Alkaloids of the pyrrolidine group
4 Alkaloids of the quinoline group
5 Alkaloids of the isoquinoline group
6. Alkaloids of the phenanthrene group
7 Alkaloids of the purine group (These have already been treated on pp 339 *et seq*)

Like every classification this is somewhat arbitrary It may be objected that the alkaloids atropine and cocaine, treated under the pyrrolidine group, also contain a pyridine nucleus, and should therefore have been included in the pyridine group It seemed, however, more

[1] Frerichs, *Arch d Pharm*, 1903, 241, 259

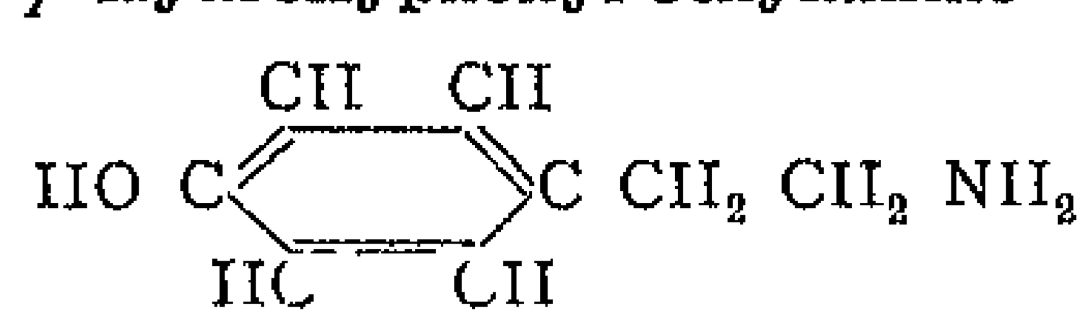
convenient to treat these compounds in a group by themselves The sixth group is termed the phenanthrene group, and under this head will be found morphine, codeine and thebaine Each of these contains a phenanthrene nucleus, but the basic complex from which they are derived has not yet been determined with certainty

I.—HYDROXY-PHENYL ALKYLAMINE AND PHENYL HYDROXY-ALKYLAMINE BASES

For **galegine**, $(CH_3)_2C\ CH\ CH_2\ N\ C(NH_2)_2$, the alkaloid of *Galega officinalis*, see E Spath and W Spitzy, *Ber*, 1925, 58, 2273

In recent years organic bases possessing phenolic character have attracted ever-increasing attention, on account of their valuable pharmacological properties Adrenaline (see p 671) has now become an important drug, the valuable properties of hordenine, present in fermenting barley, have been pointed out by Léger, and still more recently Barger has identified in *p* hydroxyphenyl ethylamine the long-sought compound to which the activity of ergot (in diseased rye seed) is mainly due

p-Hydroxyphenyl ethylamine



This compound has been shown by Barger[1] to be the active principle of ergot, in which it is present to the extent of 0 1 to 1 per cent and is accompanied by 4-β aminoethyl-glyoxaline (β-iminazyl-ethylamine) Physiologically, it has the effect of strongly increasing the blood pressure It may be isolated from the aqueous extract of ergot by shaking out with amyl alcohol, and crystallises in white needles or leaflets, m p 160°, b p 161° to 163°/2 mm pressure *p*-Hydroxyphenyl-ethylamine may be synthesised by various methods, *e g* benzyl cyanide on reduction yields phenyl ethylamine, the benzoyl derivative of which is converted into the hydroxy-phenyl compound by nitration, followed by reduction and diazotisation On removing the protective benzoyl group by hydrolysis, *p*-hydroxyphenyl-ethylamine is obtained[2]

$$C_6H_5\ (CH_2)_2NH\ COC_6H_5 \longrightarrow NO_2\ C_6H_4(CH_2)_2\ NH\ COC_6H_5 \longrightarrow$$
$$NH_2\ C_6H_4(CH_2)_2\ NH\ COC_6H_5 \longrightarrow HO\ C_6H_4(CH_2)_2NH\ COC_6H_5 \longrightarrow$$
$$HO\ C_6H_4(CH_2)_2\ NH_2$$

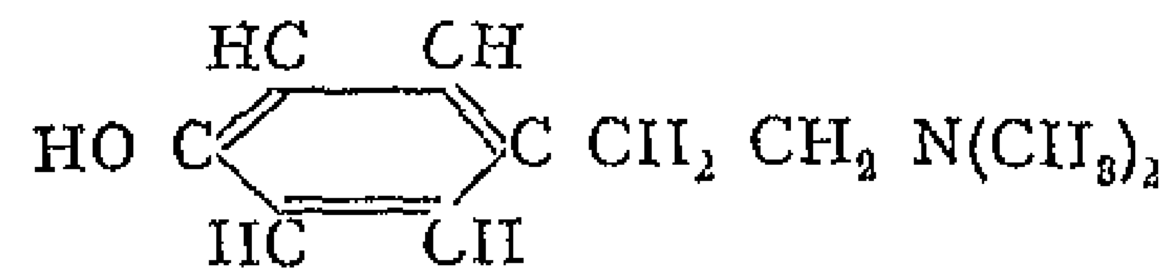
A better yield is obtained by condensing anisaldehyde with nitro-

[1] G Barger, *J C S*, 1909, 95, 1123 [2] Barger and Walpole, *J C S*, 1909, 95, 1720

methane to form *p*-methoxy-nitrostyrole, which is then reduced and the methyl group removed with hydriodic acid [1]

$$CH_3O\,C_6H_4\,CHO + H_3C\,NO_2 \longrightarrow CH_3O\,C_6H_4\,CH\,CH\,NO_2 \longrightarrow$$
$$CH_3O\,C_6H_4\,CH_2\,CH_2\,NH_2 \longrightarrow HO\,C_6H_4\,CH_2\,CH_2\,NH_2$$

Hordenine, *p*-Hydroxyphenyl-dimethylethylamine



Hordenine is present in the embryo of barley The researches which led to its discovery were prompted by the use made of germinating barley in southern France and some of the French colonies as a remedy for diarrhœa, dysentery and cholera, and the fact established later that cholera germs do not develop in an aqueous extract of germinating barley Hordenine is prepared by extracting air-dried malt with alcohol, it boils at 173° to 174° (11 mm pressure), and forms crystals of melting-point 117 5°, which are soluble in water, alcohol and ether Hordenine sulphate raises the blood pressure and increases the flow of urine It is a remedy for diarrhœa and dysentery, and in general gives good results in cases where barley can be used with success

On methylation by means of dimethyl sulphate, followed by oxidation with potassium permanganate in alkaline solution, hordenine is converted into anisic acid When degraded by Hofmann's method it yields trimethylamine The formula deduced in this manner has been confirmed by synthesis Hordenine was first synthesised by Barger [2] from phenylethyl alcohol, in the following stages .

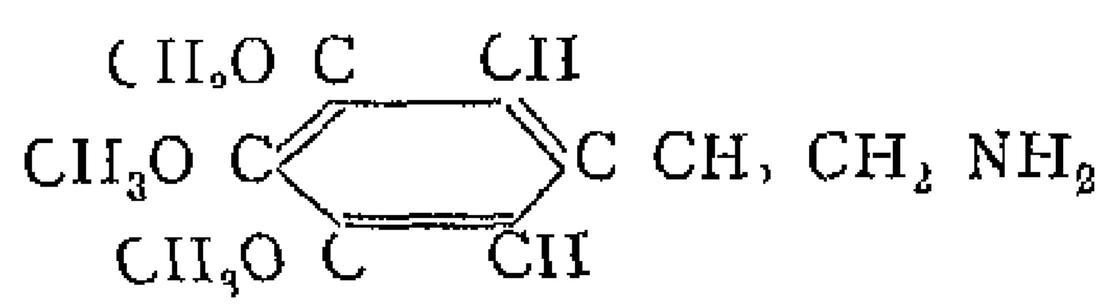
$$C_6H_5\,CH_2\,CH_2\,OH \xrightarrow{PCl_5} C_6H_5\,CH_2\,CH_2\,Cl \xrightarrow{(CH_3)_2NH} C_6H_5\,CH_2\,CH_2\,N(CH_3)_2$$
$$\xrightarrow{HNO_3} p\,NO_2\,C_6H_4\,CH_2\,CH_2\,N(CH_3)_2 \longrightarrow NH_2\,C_6H_4\,CH_2\,CH_2\,N(CH_3)_2$$
$$\xrightarrow{HNO_2} OH\,C_6H_4\,CH_2\,CH_2\,N(CH_3)_2$$

Phenolic bases of this type but of higher molecular weight, in which the $N(CH_3)_2$-groups are further removed from the benzene ring than in hordenine, have also been synthesised [3] If the phenolic hydroxyl group is displaced from the para- to the ortho-position the physiological action is much weakened [4]

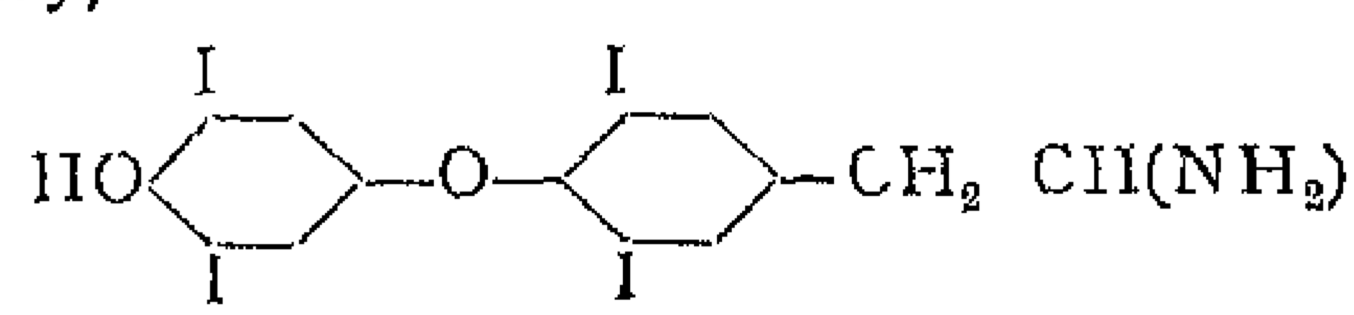
[1] K W Rosenmund, *Ber*, 1909, 42, 4778 For the preparation of other bases of this type, see *Ber*, 1910, 43, 189 [2] Barger, *J C S*, 1909, 95, 2193 [3] J v Braun and Deutsch, *Ber*, 1912, 45, 2504 [4] J. v Braun and O Bayer, *Ber*, 1924, 57, 913

Anhaline and Mezcaline

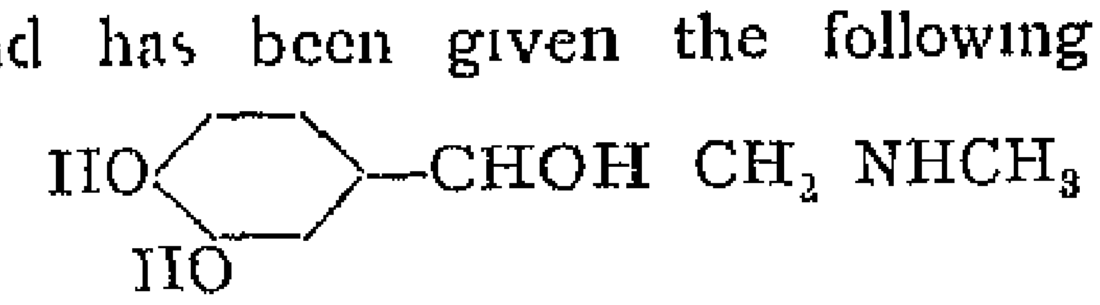
From the cactus of the Anhalonium family, which grows in North America and is used by the natives as an intoxicant, a number of basic substances have been isolated, viz, *anhaline*, *mezcaline*, *anhalamine*, *anhalonidine*, *pellotine*, *anhalonine* and *lophophorine* Most of these compounds are of unknown composition, although it seems probable from the work of E Spath[1] that anhaline is identical with hordenine The same investigator has synthesised **mezcaline** and shown it to possess the following structure[1]



Spath has also suggested formulæ for other alkaloids of the anhalonium family, for which reference should be made to the original paper

Thyroxine,  is a phenolic amino-acid containing iodine which is present in combination with protein in the hormone of the thyroid gland It was first isolated from the latter source by Kendall The structure of thyroxine was established by the synthesis of Harington and Barger[2]

Adrenaline, $C_9H_{13}O_3N$, is the active principle (hormone) of the adrenal gland, which brings about increase in the blood pressure It contains the catechol complex and has been given the following structure



When catechol is heated with chloracetic acid in the presence of phosphorus oxychloride, chloracetocatechol, $(HO)_2C_6H_3 \cdot CO \cdot CH_2Cl$, is formed On treatment with methylamine the latter yields $(HO)_2C_6H_3 \cdot CO \cdot CH_2 \cdot NHCH_3$, which on reducing the keto group to —CHOH gives racemic adrenaline[3] having the same constitution as the natural laevorotatory product, although physiologically less active

Ephedrine and Pseudo ephedrine[4]

$$C_6H_5 \cdot \underset{\displaystyle OH}{\underset{|}{CH}} - \underset{\displaystyle NHCH_3}{\underset{|}{CH}} - CH_3$$

1-Phenyl-2-methylaminopropane-1-ol — Ephedrine and pseudo ephedrine are two bases with mydriatic properties occurring in

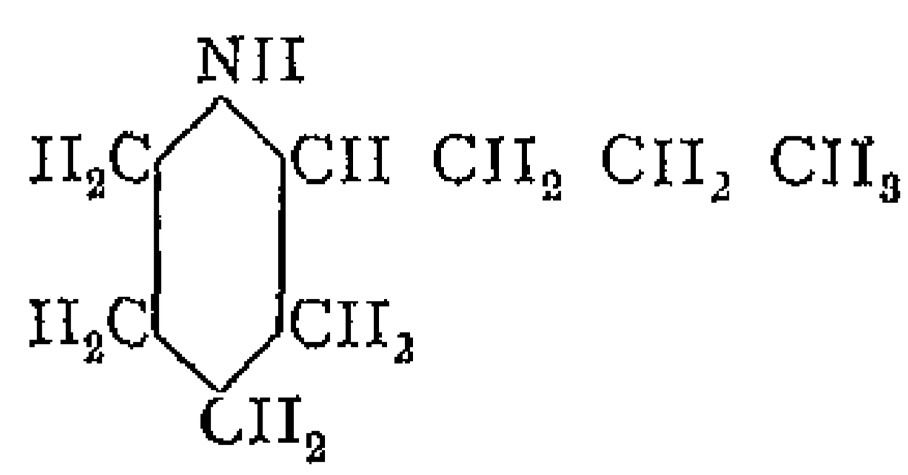
[1] *Monats*, 1919, 40, 129 C, 1919, III, 434 [2] Harington and Barger, *Biochem J*, 1927, 21, 169 See also *Some Applications of Organic Chemistry to Biology and Medicine*, by George Barger (McGraw Hill Book Co, New York, 1930) [3] Stolz, *Ber*, 1904, 37, 4147 Dakin, *Proc Roy Soc*, 1905, B 76, 491, 498 [4] E Späth and G Koller, *Ber*, 1925, 58, 1268

Ephedra vulgaris. They are optical isomerides, and under the influence of heat the former changes into the latter. Ephedrine is a white crystalline substance, which boils about 225° with decomposition. **Mydrine**, formed by the combination of ephedrine and homatropine (see p. 697), rapidly brings about a considerable degree of mydriasis and is employed medicinally for this purpose.

II.—ALKALOIDS OF THE PYRIDINE GROUP

Among the large number of alkaloids containing a pyridine nucleus, only coniine, conhydrine, *pseudo*-conhydrine, γ-coniceine, ricinine and piperine will be treated here.

α-**Coniine**, dextro-2-*n*-propyl-piperidine.



Coniine is of special interest from the historical standpoint, because the synthesis of this compound by Ladenburg, which was commenced in 1886 and finished at a later date, constituted the first complete synthesis of a naturally occurring alkaloid.[1] The reason for the early synthesis of the compound lies in its simple constitution. Of the numerous alkaloids known to-day, very few are built up from carbon, hydrogen and nitrogen alone, and of these coniine possesses the simplest structure.

Coniine is present in hemlock, *Conium maculatum*, especially in the seeds, in which it is accompanied by N-methyl-coniine, γ-coniceine, conhydrine, and pseudo-conhydrine. It is a colourless, very poisonous liquid, b.p. 167°.

Degradation of Coniine

A. W. Hofmann subjected coniine to certain reactions which he had previously carried out with piperidine, and found that the two compounds behaved in a similar manner.

1. *Exhaustive methylation* of coniine gave a product having the composition of a dimethyl-coniine, $C_8H_{15}(CH_3)_2N$, and also a hydrocarbon conylene, of the formula C_8H_{14}.

$$\underset{\text{Coniine}}{C_8H_{17}N} \longrightarrow C_8H_{16}(CH_3)NCH_3I \longrightarrow C_8H_{16}(CH_3)NCH_3OH \xrightarrow{-H_2O}$$

$$C_8H_{15}(CH_3)_2N \longrightarrow C_8H_{15}(CH_3)_3N\cdot OH \longrightarrow \underset{\text{Conylene}}{C_8H_{14}} + N(CH_3)_3 + H_2O$$

[1] *Ber.*, 1889, 22, 1403.

Hofmann observed that conylene differed from piperylene by the same atomic complex, C_3H_6, as coniine from piperidine, and hence suggested that coniine might be a homologue of piperidine. Shortly afterwards, Königs put forward the surmise that coniine was a propyl-piperidine. This view was confirmed by Hofmann's distillation of the alkaloid with zinc dust.

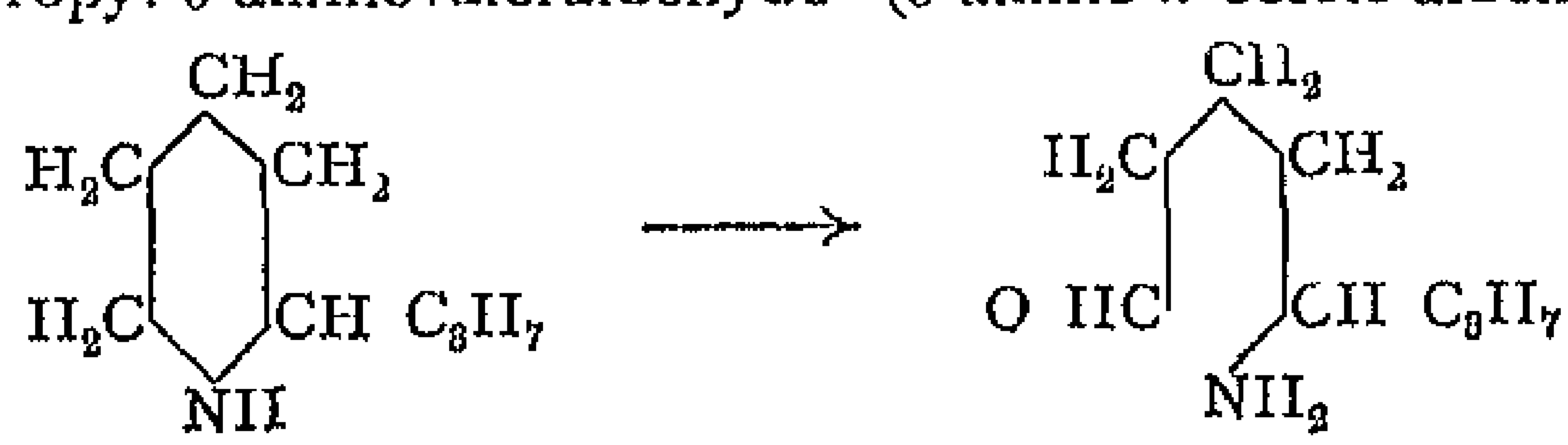
2. The *distillation with zinc dust* was undertaken in the expectation of obtaining from coniine a compound richer in hydrogen. In actual practice it was found that hydrogen was removed,[1] and the compound $C_8H_{17}N$ converted into one of the composition $C_8H_{11}N$. The new base, *conyrine*, was easily recognised as a derivative of pyridine, and being six atoms poorer in hydrogen than coniine, appeared to stand to the latter in the same relationship as pyridine to piperidine.

Any doubt as to the nature of conyrine was resolved by its conversion into picolinic acid or 2-pyridine-carboxylic acid (see p. 644) on oxidation.

From this it followed that conyrine must be either 2-propyl- or 2-isopropyl-pyridine, and coniine therefore 2-propyl- or 2-isopropyl-piperidine. The choice between these two alternatives was decided in favour of the normal propyl structure by Hofmann's discovery that coniine, on reduction with hydriodic acid, gave ammonia and normal octane. Had an isopropyl group been present, this could not have occurred without intramolecular rearrangement.

The constitution of coniine as 2-propyl-piperidine was finally confirmed by synthesis.

3. The *oxidation of coniine with hydrogen peroxide* led to the formation of δ-propyl-δ-aminovaleraldehyde[2] (δ-amino *n* octoic aldehyde).



Synthesis of Coniine

The synthesis of coniine was accomplished by Ladenburg[3] with the aid of the following three reactions: (*a*) introduction of side groups into pyridine by heating pyridine alkiodides under pressure (see p. 640), (*b*) condensation of α- and γ-methyl-pyridines with aldehydes (p. 641 *et seq.*), (*c*) conversion of pyridines into piperidines by reduction with sodium and alcohol. The complete synthesis of coniine proceeds in the following stages.

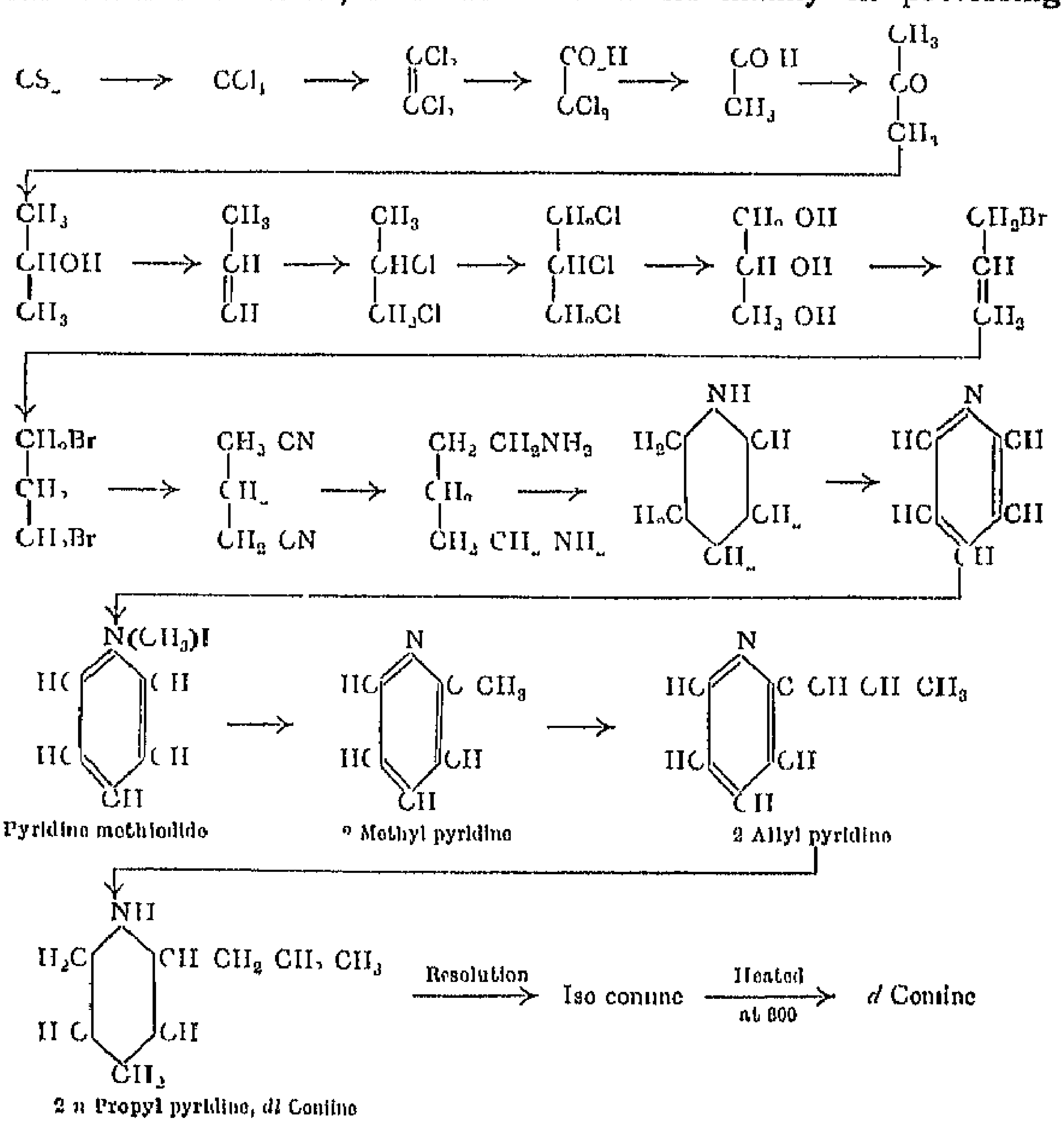
Carbon disulphide, which can be prepared from its elements, is

[1] Hofmann, *Ber.*, 1884, **17**, 825. [2] Wolffenstein, *Ber.*, 1895, **28**, 1460. Butyryl butyric acid (δ propyl ketobutyric acid) is also formed. [3] *Ber.*, 1889, **22**, 1403; 1906, **39**, 2486. Compare also Lénart, *Ann.*, 1915, **410**, 95.

converted through the various intermediate compounds shown below into trimethylene bromide The latter, by way of trimethylene cyanide, yields pentamethylene diamine, from which piperidine is obtained by splitting off ammonia Piperidine may be oxidised to pyridine, and this with methyl iodide gives the addition compound pyridine methiodide, which at 300° is transformed into the hydriodide of α-picoline On heating picoline itself with paraldehyde to a high temperature it gives α-allyl-pyridine, which by reduction is converted into inactive coniine

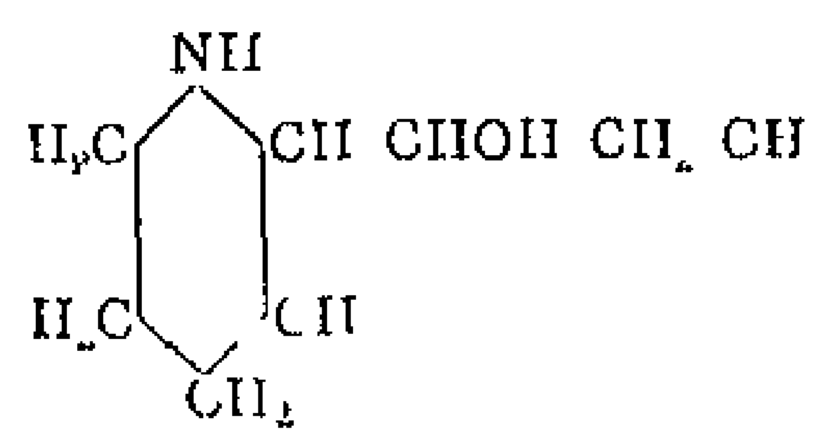
The racemic base may be resolved by means of *d*-tartaric acid On crystallising a solution of *i*-coniine *d*-tartrate the first salt to separate is *d*-coniine *d*-tartrate, which is then removed and decomposed with alkali

Synthetic coniine as thus obtained is identical in most respects with natural *d*-coniine, from which it differs mainly in possessing

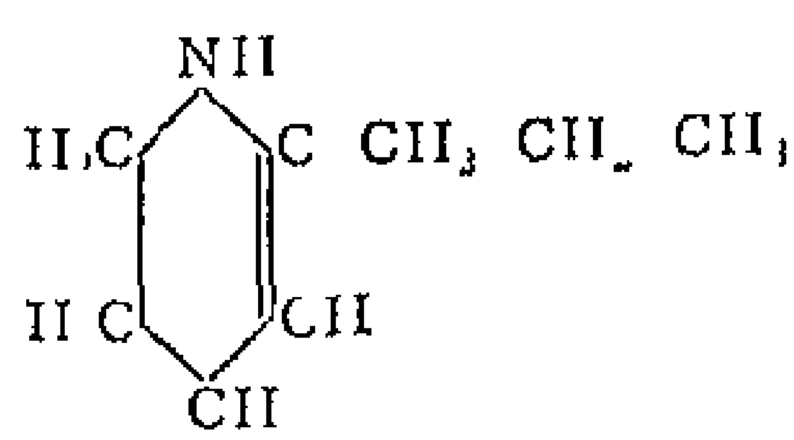


a slightly higher rotation (by about 4°) The synthetic product was at first believed to be an isomeric *iso*-coniine, which on heating alone or with alkali gave a product identical with the natural alkaloid Recent work indicates that *iso*-coniine is merely an impure form of coniine [1]

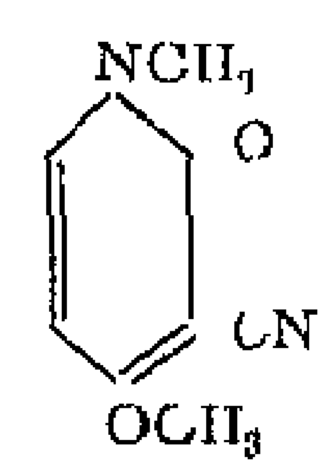
Conhydrine and **pseudo conhydrine** are also present in plants of the hemlock family [2] The former, m p 118° and b p 225° to 226°, crystallises from ether in colourless leaflets, the latter, m p 101° to 102 and b p 229° to 231°, is a deliquescent crystalline powder A careful investigation of conhydrine has shown it to be an optically active 2 ethyl piperidyl alkine [3] of the formula



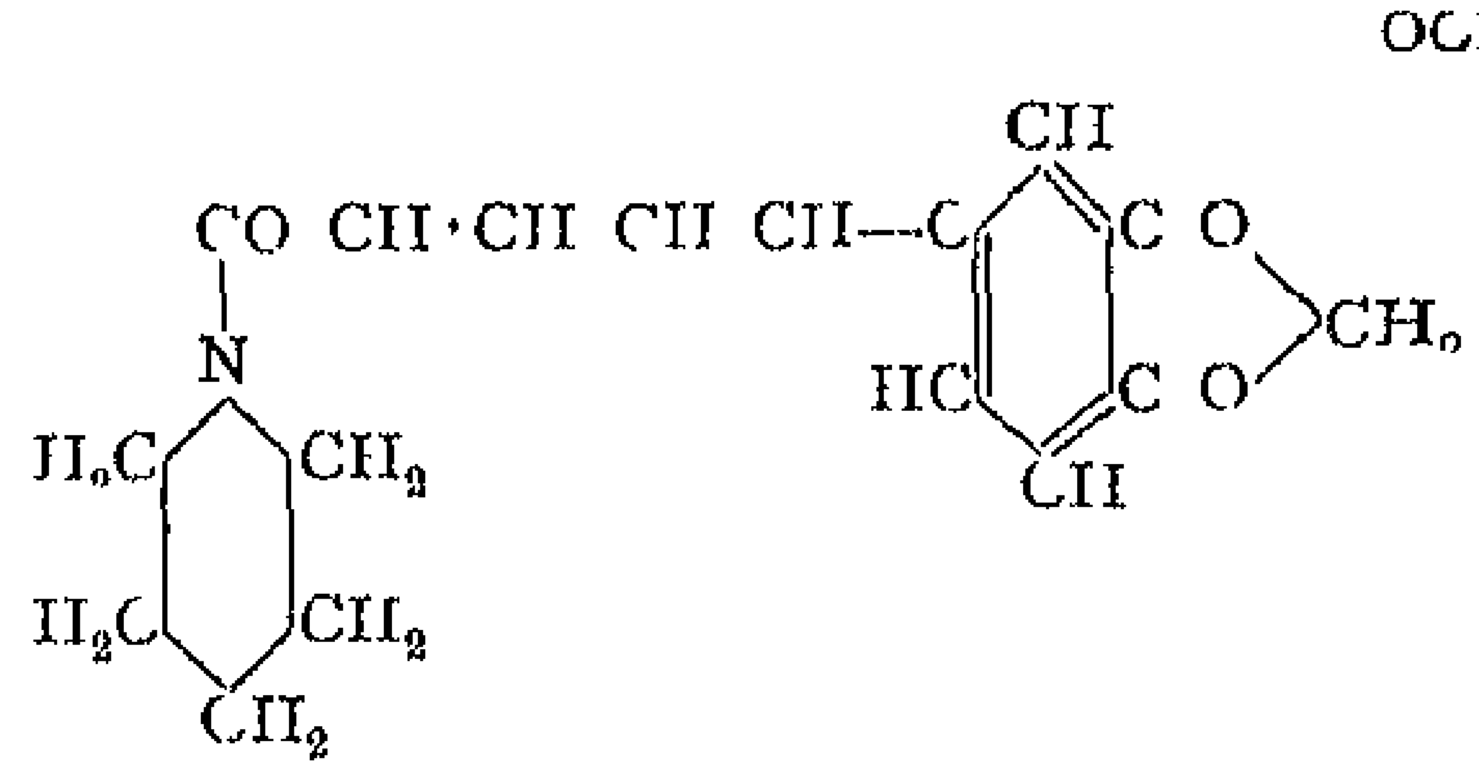
Pseudo conhydrine is a hydroxy coniine in which the hydroxyl group must be attached to the ring [4]

γ Coniceïne,  may be prepared directly from hemlock and also by synthesis [5] Various structural isomerides of this substance, which cannot be described here, are obtained by the removal of the elements of water from conhydrine and pseudo conhydrine, or of hydrogen iodide from their iodides

Ricinine, the alkaloid of the castor oil plant, has the structure of a 1 *methyl* 3 *cyano* 4 *methoxy* 2 *pyridone* [6] This has been confirmed by synthesis



Piperine,



[1] K Hess and Weltzien, *Ber*, 1920, 53B, 139 [2] For the separation of the alkaloid bases (coniine, methyl coniine, γ coniceine, conhydrine, and pseudo conhydrine) present in hemlock, compare J v Braun, *Ber*, 1905, 38, 3708 [3] Löffler and Tschunke, *Ber*, 1909, 42, 929 [4] Löffler, *Ber*, 1909, 42, 116 [5] S Gabriel, *Ber*, 1909, 42, 4059 [6] E Späth and G Koller, *Ber*, 1923, 56, 880, 2454

The fruit and seeds of different species of pepper contain, in addition to a terpene, a comparatively large proportion (7 to 9 per cent) of piperine It was first discovered in 1819 by Oersted, and crystallises in monoclinic columns, m p 128° to 129°

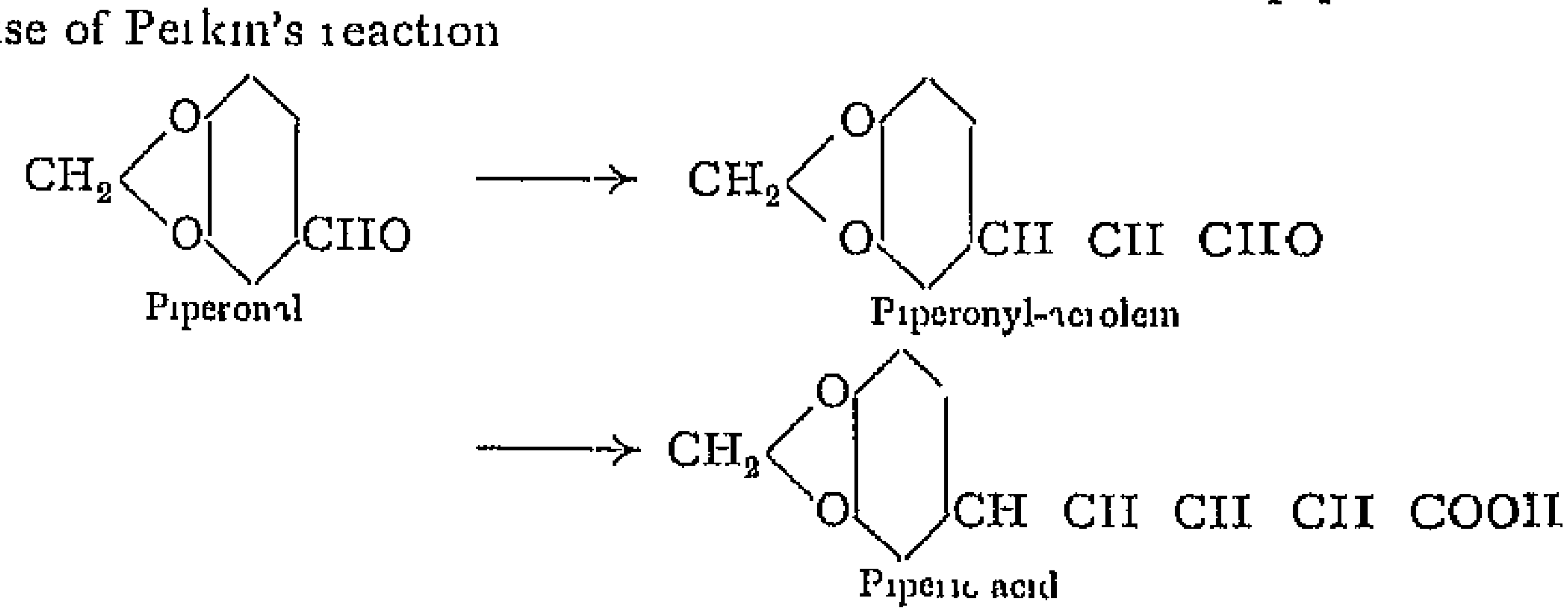
When boiled with alcoholic potash it breaks down into piperidine and piperic acid

$$\underset{\text{Piperine}}{C_{17}H_{19}NO_3} + H_2O = \underset{\text{Piperidine}}{C_5H_{11}N} + \underset{\text{Piperic acid}}{C_{12}H_{10}O_4}$$

Hence it was concluded that piperine is a compound of amide type built up from piperidine and piperic acid This view was confirmed by the partial synthesis of piperine[1] on heating piperidine in benzene solution with the chloride of piperic acid

$$\underset{\text{Piperidine}}{C_5H_{10}NH} + \underset{\text{Piperic acid chloride}}{ClOC\ C_{11}H_9O_2} = \underset{\text{Piperine}}{C_5H_{10}N\ OC\ C_{11}H_9O_2} + HCl$$

The constitution and synthesis of piperidine have been described on p 638 *et seq*, and the structure of piperic acid was solved by Fittig and confirmed by the following synthesis of Ladenburg and Scholtz[2] Piperonal (see p 433) was condensed with acetaldehyde in the presence of aqueous alkali to give the unsaturated aldehyde, piperonyl-acrolein, the latter was then converted into piperic acid by use of Perkin's reaction

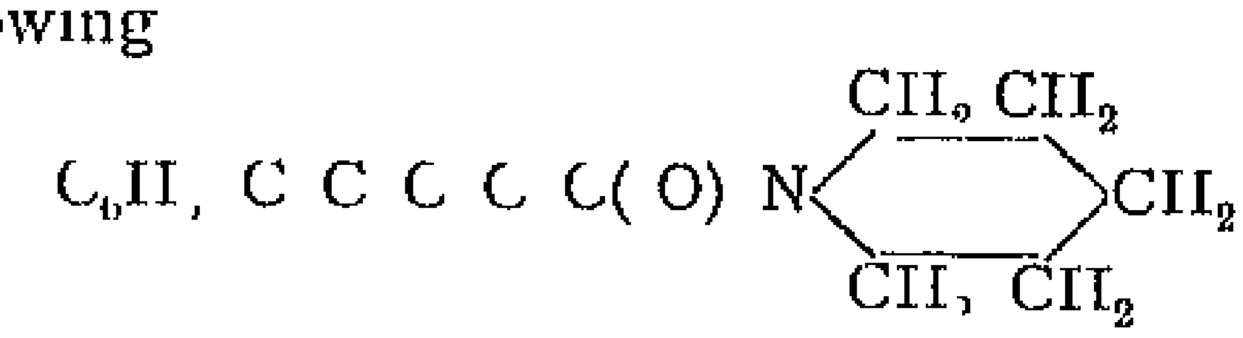


Consequently the above preparation of piperine from its hydrolysis products, piperidine and piperic acid, completes the synthesis of this alkaloid

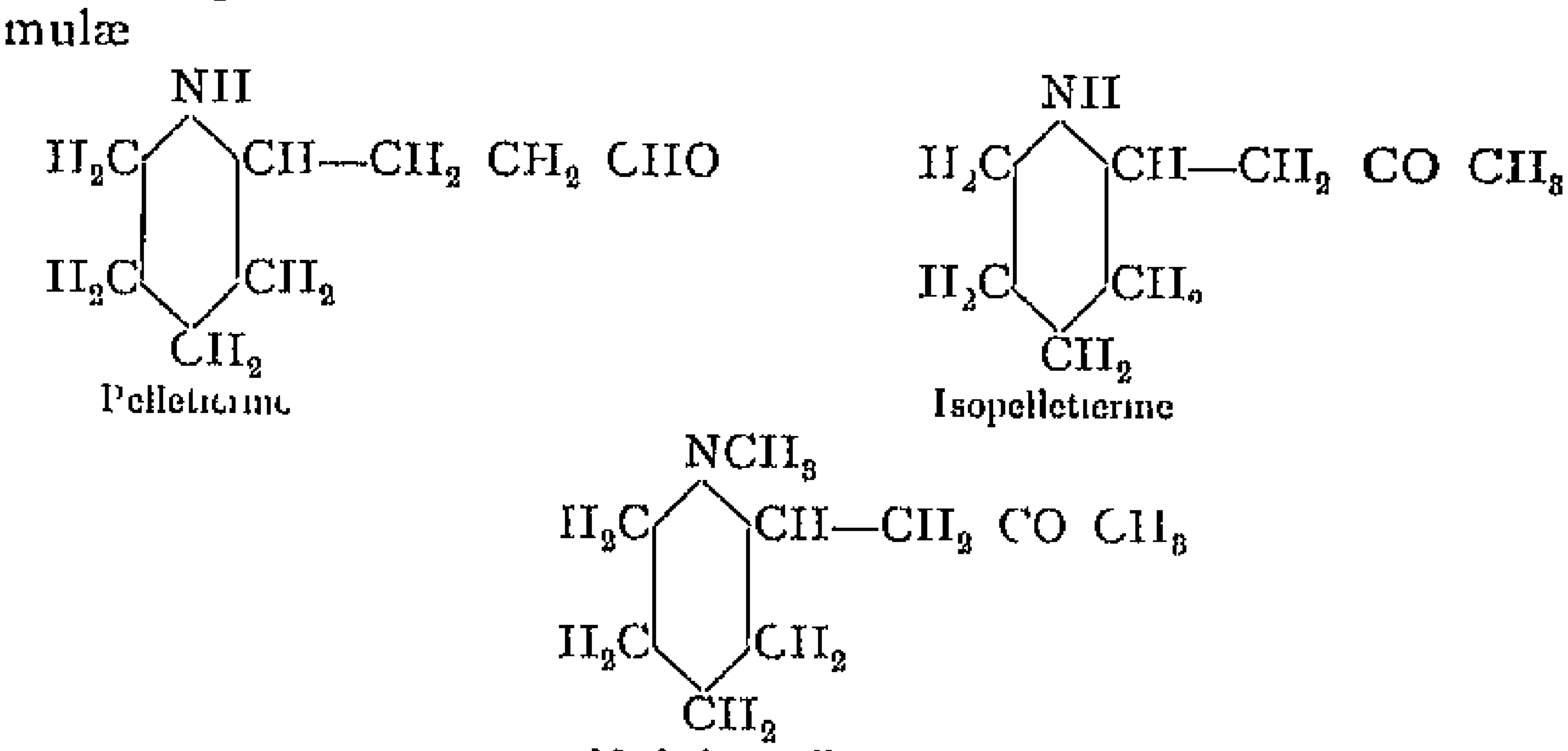
Owing to the rising price of pepper, experiments have been directed towards an artificial product of similar taste An actual synthesis of piperine is out of the question owing to the cost of starting materials, but information as to the relationship between constitution and pepper-like taste has been gained by the work of H Staudinger[3] It appears that the molecule of piperine may undergo considerable changes without losing the characteristic taste An essential condition is the acid-amide linking of piperidine with a fatty-aromatic acid

[1] Ber, 1892, 25, 1390 *Ann*, 1871, 159, 142 [2] *Ber*, 1894, 27, 2858 [3] H Staudinger ...kers, *Ber*, 1923, 56, 699, 711 H Rheinboldt, *Ber*, 56, 1228 C Riccomanni, *C*, 9

radical, and the most pronounced resemblance to pepper was observed with derivatives of δ-phenyl-*n*-valeric acid. The most effective structure is thus the following:



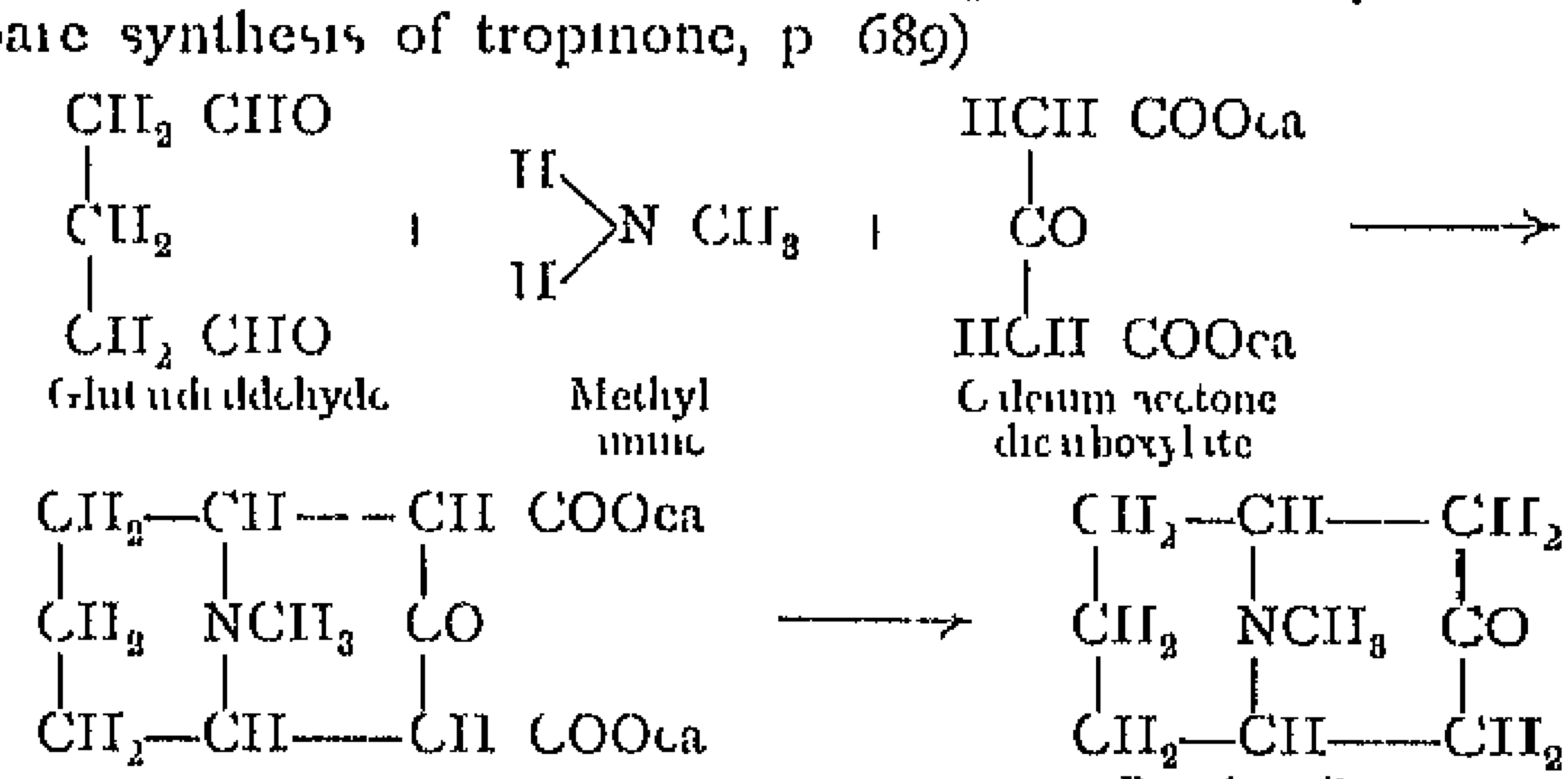
Alkaloids of the Pomegranate Bark.—The bark of the pomegranate tree (*Punica Granatum* L.) contains several alkaloids, to the presence of which is due its long-known usefulness as a vermicide. These alkaloids, viz., *pelletierine* and *isopelletierine* of the formula $C_8H_{15}NO$, *methyl-isopelletierine* (1-*methyl*-2-*acetonyl-piperidine*) of the formula $C_9H_{17}NO$, and *pseudo-pelletierine*, $C_9H_{15}NO$, have been examined in detail by Hess, and later by Meisenheimer.[1] Their constitutions can now be regarded as established in accordance with the following formulæ:



Pelletierine Isopelletierine

Methyl-isopelletierine

Pseudo-pelletierine has recently been synthesised by Menzies and Robinson[2] in a simple manner from glutaric aldehyde as follows (compare synthesis of tropinone, p. 689):



Glutardialdehyde Methylamine Calcium acetone dicarboxylate

Pseudo-pelletierine

[1] K. Hess and co-workers, *Ber.*, 1920, **53**, 129; *Ann.*, 1925, **441**, 101. J. Meisenheimer and F. Mahler, *Ann.*, 1928, **462**, 301. [2] R. C. Menzies and R. Robinson, *J. C. S.*, 1924, **125**, 2163.

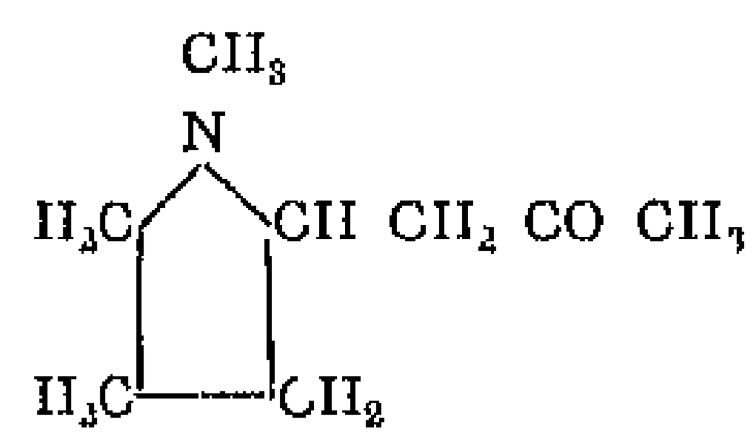
III.—ALKALOIDS OF THE PYRROLIDINE GROUP AND DERIVATIVES OF TROPANE

In this group are included hygrine and cuskhygrine, nicotine, atropine, hyoscyamine, cocaine, tropacocaine and others. Since the five-membered pyrrolidine ring is more easily formed than the corresponding six-membered ring, the production of alkaloids of the pyrrolidine type in plants is not surprising. In all probability a number of other alkaloids, the constitution of which is still unknown, will eventually be found to fall within this class.

Hygrines

From South American coca, obtained from truxillo and cusko leaves, Liebermann[1] succeeded in isolating two bases, hygrine ($C_8H_{15}NO$) and cuskhygrine ($C_{13}H_{24}N_2O$). Both of these are amino ketones, which on oxidation with chromic acid are converted into hygrinic acid (*cf.* p. 579).

Hygrine, 1-methyl-2-acetonyl-pyrrolidine, possesses the following structure:

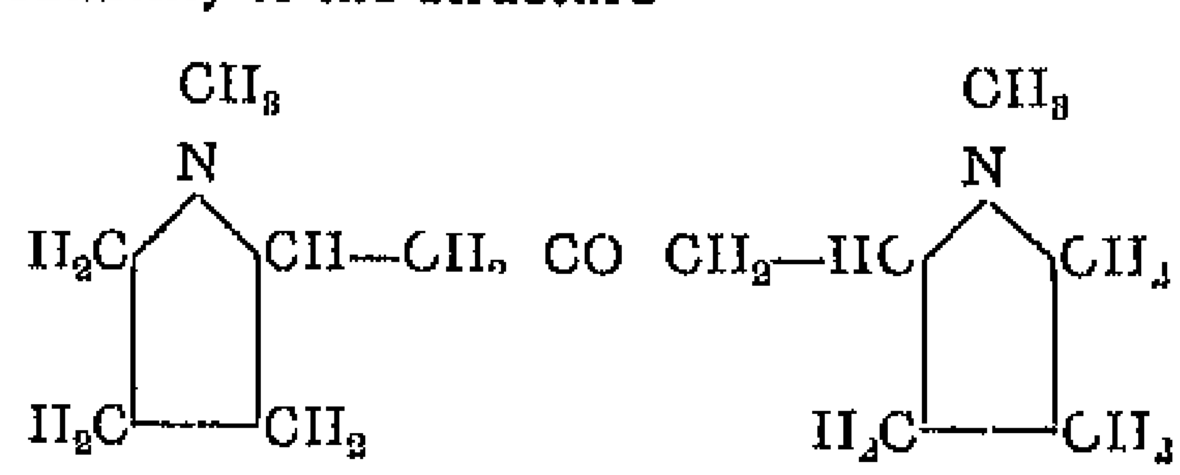


which is confirmed by the formation of a monoxime, the degradation of hygrine to hygrinic acid (1-methyl-pyrrolidine-2-carboxylic acid) and by the synthesis of the base.[2]

Hygrine is found more particularly in Peruvian cusko leaves, in which it occurs up to 0.2 per cent. It is a liquid which darkens in air and boils at 193° to 195° under ordinary pressure.

Cuskhygrine

Cuskhygrine, $C_{13}H_{24}N_2O$, is simply related to hygrine, $C_8H_{15}NO$, one hydrogen atom of the latter being replaced by the monovalent 1-methyl-pyrrolidine radical. It conforms in all probability to the structure[3]

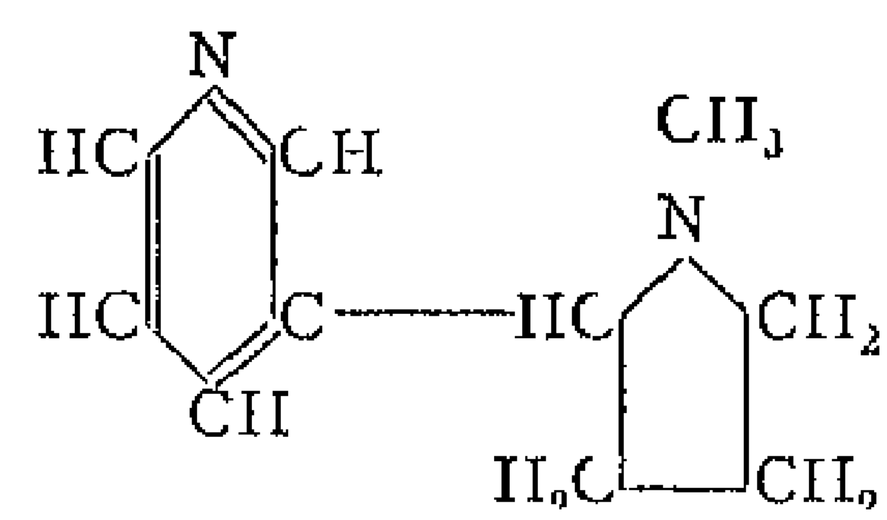


Cuskhygrine is present in the crude hygrine obtained from cusko leaves, of which it constitutes the higher boiling main fraction. It is a colourless oil of faint odour, boiling at 185° under 32 mm. pressure. Attempts have been made to synthesise this substance but have not yet been brought to a successful conclusion.[4]

[1] C. Liebermann and Giesel, *Ber.*, 1897, 30, 1113. K. Hess, *Ber.*, 1913, 46, 3113, 4104. [2] *Ber.*, 1900, 33, 1161. [3] See *Ann. Rep. Chem. Soc.*, 1925, p. 134. [4] Hess and Fink, *Ber.*, 1915, 48, 1986.

Nicotine

1-*Methyl-2-β pyridyl-pyrrolidine*,



Nicotine is found combined with malic acid and citric acid in the leaves of tobacco (*Nicotiana tabacum*)

The above constitutional formula was advanced by Pinner in 1893, and finally confirmed by the synthesis of the alkaloid by A Pictet [1]

Synthesis of Nicotine [1]

Starting from β-aminopyridine, the synthesis of nicotine involved the following eight changes

β Aminopyridine $\xrightarrow{\text{distillation with mucic acid}}$

1 β Pyridyl pyrrole $\xrightarrow{\text{strongly heated}}$

2 β Pyridyl pyrrole $\xrightarrow{\text{potass salt with } CH_3I}$

1 Methyl 2 β pyridyl pyrrole methiodide $\xrightarrow{\text{distillation with lime}}$

1 Methyl 2 β pyridyl pyrrole (nicotyrine) $\xrightarrow{\text{action of I}}$

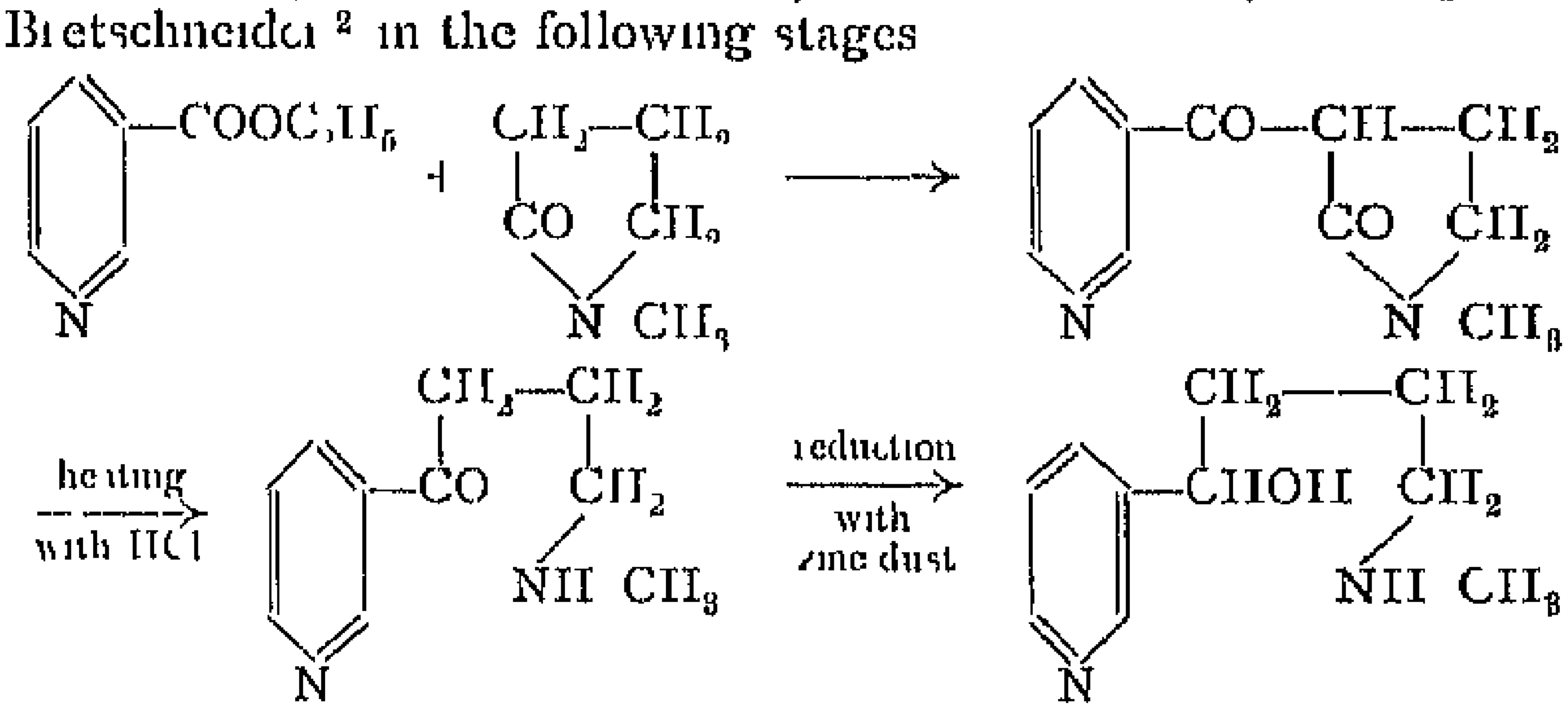
Iodo nicotyrine (1 methyl 2 β pyridyl 4 iodopyrrole) $\xrightarrow{\text{reduction}}$

Dihydro nicotyrine (1 methyl 2 β pyridyl pyrroline) $\xrightarrow[\text{with Sn and HCl}]{\text{red of the perbromide}}$

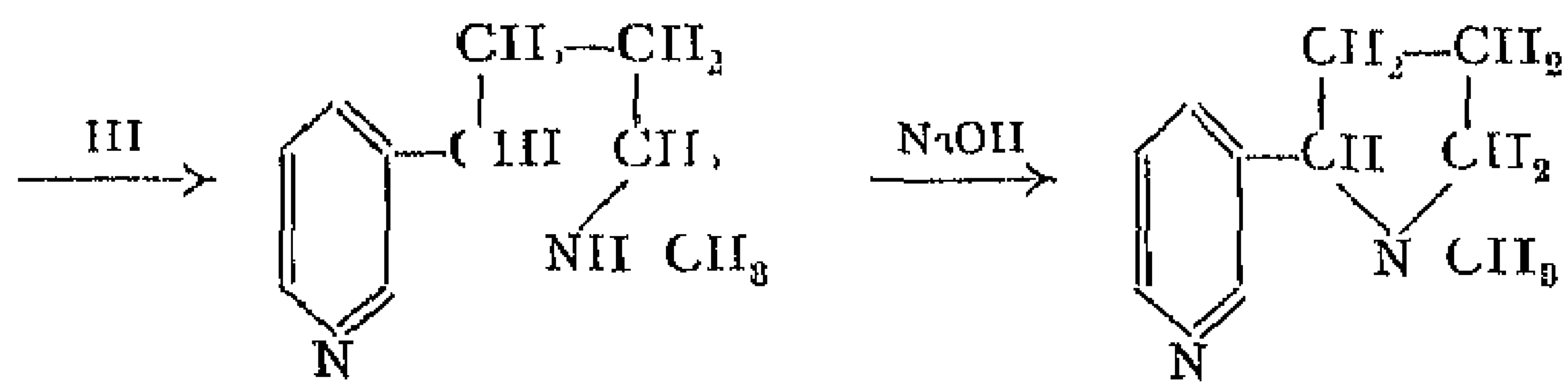
Tetrahydro nicotyrine (*dl* nicotine) $\xrightarrow[\text{tartaric acid}]{\text{resolution with}}$

l Nicotine

A further synthesis has recently been effected by E. Späth and H Bretschneider [2] in the following stages



[1] Pictet and Rotschy, *Ber.*, 1904, 37, 1225 [2] *Ber.*, 1928, 61, 327



Note—The first condensation in this synthesis is brought about in the presence of sodium ethoxide, giving a product which, on being heated with fuming hydrochloric acid, is hydrolysed with loss of carbon dioxide

l-*Nicotine*

The naturally occurring alkaloid is laevorotatory, $[\alpha]_D^{20} = -166.4°$, and, as indicated above, can also be obtained by resolving the synthetic *dl*-nicotine with the aid of tartaric acid According to the kind of tobacco, the nicotine content varies from 0.6 to 8 per cent (pipe tobacco 0.518 to 0.854 per cent, cigars 0.801 to 2.887 per cent) In general, the finer kinds of tobacco contain smaller proportions of nicotine

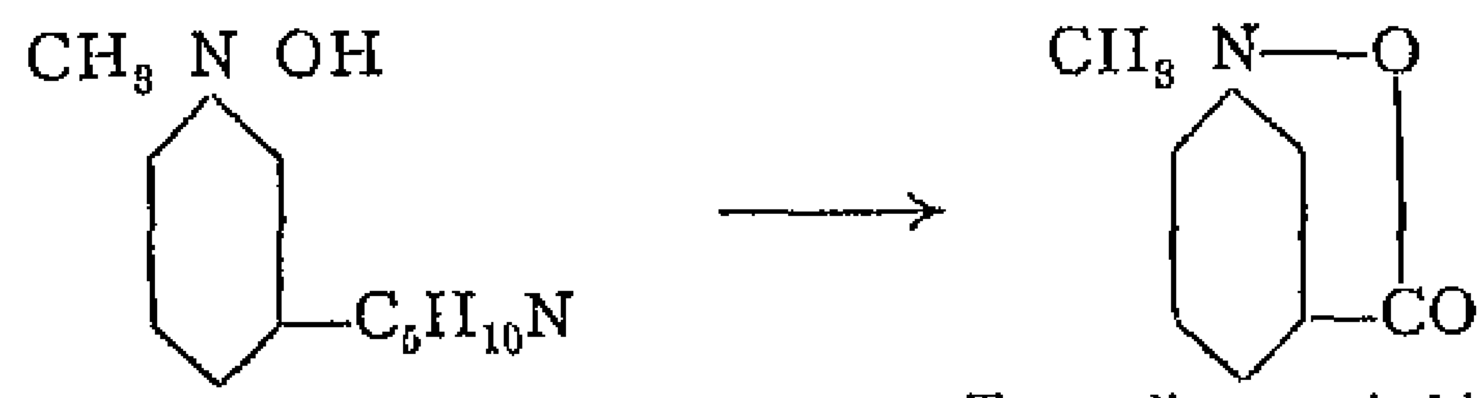
The alkaloid is conveniently obtained from extract of tobacco, which is prepared industrially by extracting a raw tobacco of high nicotine content with cold water and concentrating the solution The extract is used for the impregnation of chewing tobacco, and contains about 8 to 10 per cent of nicotine It is first diluted with water, and freed from hydrocarbons by the addition of acid and extraction with ether The solution is then made alkaline, and the free nicotine repeatedly extracted with ether

Freshly prepared *l*-nicotine is a colourless oil, which dissolves readily in water, has a burning taste, and is very poisonous When pure, it has an unpleasant, stupefying odour, unlike that of tobacco It can only be distilled without decomposition *in vacuo* or in a current of hydrogen, in air it rapidly turns brown and resinifies Nicotine boils at 246.2° under 730 mm pressure It forms diacid salts which do not crystallise well, these dissolve readily in water and rotate the plane of polarisation to the *right*

Nicotine yields two *mono-methiodides*[1] One of these isomerides is obtained as a syrupy mass on bringing together equimolecular amounts of nicotine and methyl iodide The second results when nicotine is first treated with a molecular equivalent of hydriodic acid and then with methyl iodide under these conditions the methyl iodide unites with the less basic nitrogen atom of the pyridine ring By converting the methiodide into the hydroxide and oxidising the latter with potassium permanganate, Pictet[1] obtained the alkaloid

[1] Pictet and Genequand, *Ber*, 1897, 30, 2117

trigonelline, which is present in the seeds of *fenugreek*, of *Strophanthus hispidus*, and other plants



Trigonelline, methyl-betaine of nicotinic acid

Conversion of l-*Nicotine into* dl-*Nicotine*

As has already been stated in the general section of this book, a number of optically active compounds can be racemised or transformed into their inactive modifications by continued heating in solution

This phenomenon has also been observed in the case of nicotine [1] On heating an aqueous solution of the monohydrochloride or sulphate of nicotine at 180° to 250° in a sealed tube, the rotation steadily diminishes and finally becomes zero

dl-Nicotine may be isolated from heated solutions of its salts in the usual manner In properties such as boiling-point, specific gravity, refractive index, smell, solubility and salt formation, it is identical with the natural *l*-rotatory alkaloid

d-*Nicotine* [2]

This was isolated in the crude state during the preparation of *l*-nicotine from the inactive synthetic compound, and purified by use of *l*-tartaric acid Its specific rotation $[\alpha]_D^{20}$ was found to be + 163 17°, and in boiling-point and other physical properties it was identical with the *l*-isomeride

d-Nicotine is less poisonous than *l*-nicotine In this respect, the different action of the two antipodes towards the animal organism may be compared to the different behaviour of optical antipodes in general towards any other optically active compound, and towards organised, as distinct from unorganised, ferments

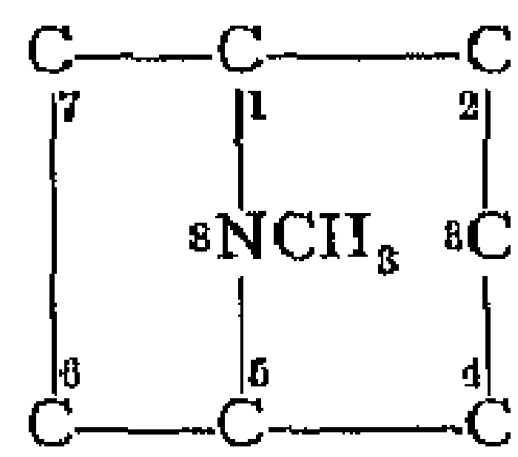
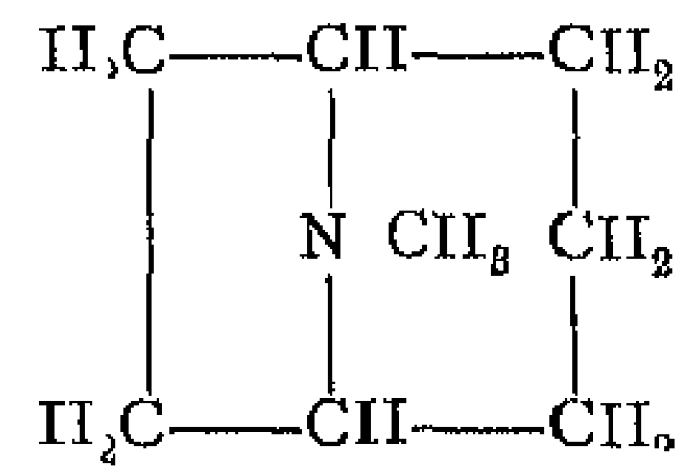
In addition to nicotine, the alkaloids [3] *nicoteine*, *nicotimine*, and *nicotelline* have been isolated from the tobacco plant

Compounds of the Tropane Series

Nomenclature.—The various alkaloids of this group contain a peculiar combination of a reduced pyrrole and a reduced pyridine ring

[1] Pictet and Rotschy, *Ber*, 1900, 33, 2353 [2] Pictet and Rotschy, *Ber*, 1904, 37, 1232
[3] Pictet and Rotschy, *Ber*, 1901, 34, 696 *Compt rend*, 132, 971 A fifth alkaloid has possibly been isolated from tobacco, *cf* *Monats*, 1902, 23, 236

(Willstätter), the periphery of the cyclic system forming a seven-membered carbon ring

I  II 

Derivatives of tropane are generally described by use of the numbering given in formula I, the compounds being referred in the customary manner to tropane (II) as parent substance

In the following list are given the older names in common use for the more important members of this group, together with the systematic names referred to tropane

Hydro tropidine	$C_8H_{15}N$	tropane
Tropine	$C_8H_{14}(OH)N$	tropanol
Tropinone	$C_8H_{13}ON$	tropanone
Tropigenine	$C_7H_{13}ON$	nortropanol
Norhydro tropidine	$C_7H_{13}N$	nortropane
Tropidine	$C_8H_{13}N$	tropene

Willstätter's[1] syntheses of tropane and tropane derivatives are based upon the alkylating action of a halogenated group on a basic group of the same molecule Just as an alkyl halide reacts with a primary amine to yield the salt of a secondary amine, or with a tertiary amine to form a quaternary ammonium salt, so with a halogenated base an intramolecular reaction may occur between the halogenated portion of the molecule and the basic group In such a case the halogen atom and the alkyl residue to which it was originally united become attached by separate valency bonds to the nitrogen atom, leading to the production of a cyclic base in which nitrogen forms part of the ring Thus a halogenated primary base yields the salt of an imine, and a tertiary compound yields a quaternary ammonium halide A reaction of this type is described by Willstätter as *intramolecular alkylation* (compare the synthesis of 2-methyl-1-dimethyl-pyrrolidinium chloride from pentenyl-dimethylamine, p 579)

Intramolecular alkylation may also lead to the formation of dicyclic bases, if the addition products of certain unsaturated monocyclic amines are used as starting material

Derivatives of tropane have been synthesised in this manner by Willstätter, starting from a base containing a cyclic system of seven carbon atoms, and having a halogen atom in one of the two δ-positions (*i e* positions 4 or 5) to the N-group (see next page)

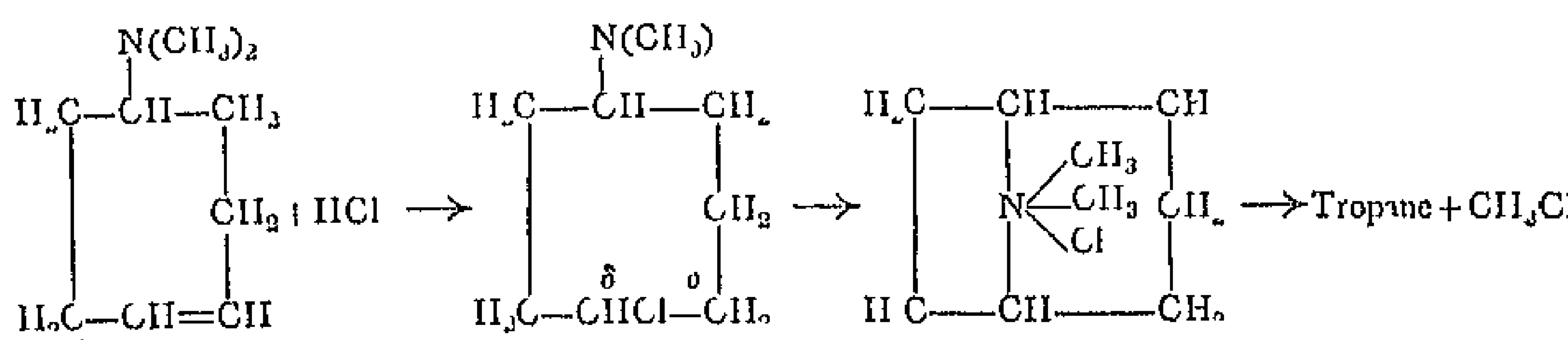
[1] *Ann*, 1901, 317, 307

Tropane, hydrotropidine (formula II, p 682), the parent substance of the tropane series, was first obtained by Ladenburg by the action of zinc dust and hydrochloric acid on tropine iodide

$$C_8H_{14}IN,HI + 2H = C_8H_{16}N,HI + HI$$

According to Willstätter, tropane is best prepared from the hydrogen halide addition products of tropidine, by reduction with zinc dust and hydrogen iodide in the cold It is also formed from tropinone by treatment with zinc dust and hydriodic acid

Willstätter[1] has synthesised tropane by two methods One of these starts from the addition compound obtained by union of Δ^4 dimethyl amino cycloheptene with hydrochloric acid When this is gently warmed, it is largely converted by intramolecular ammonium salt formation into tropane methochloride, from which, on dry distillation, tropane is obtained It is a liquid of boiling point 167°, which is sparingly soluble in cold, and still less soluble in hot water

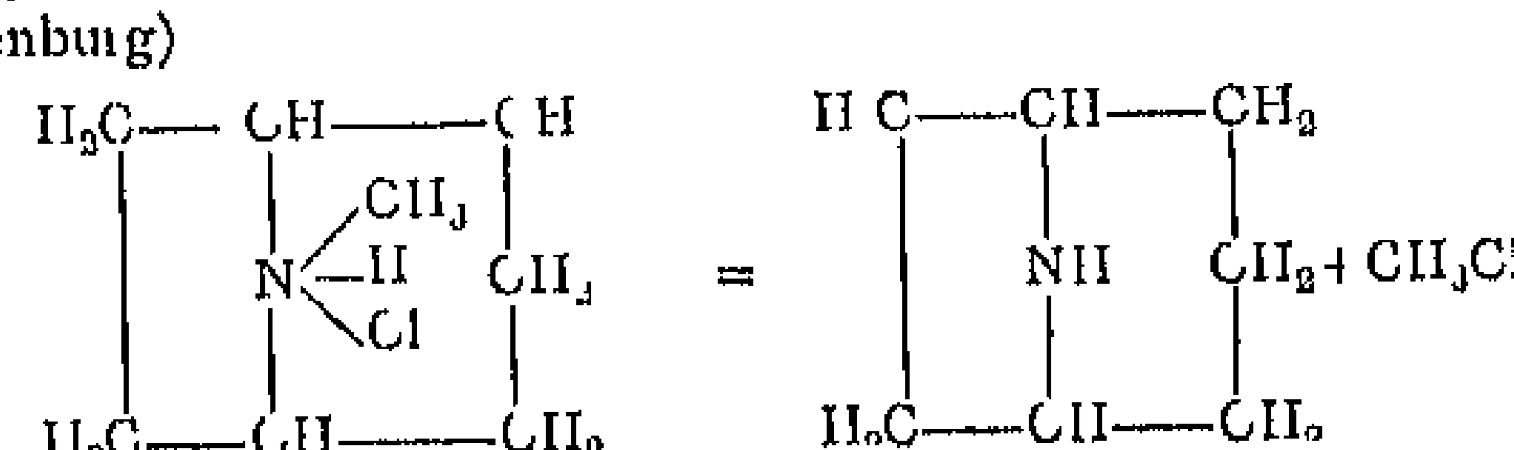


Δ^4 Dimethylamino cycloheptene

On exhaustive methylation tropane yields hydrotropilidene or cycloheptadiene, C_7H_{10}, the final stage of the degradation being as follows

$$C_7H_{11}N(CH_3)_3OH = C_7H_{10} + N(CH_3)_3 + H_2O$$

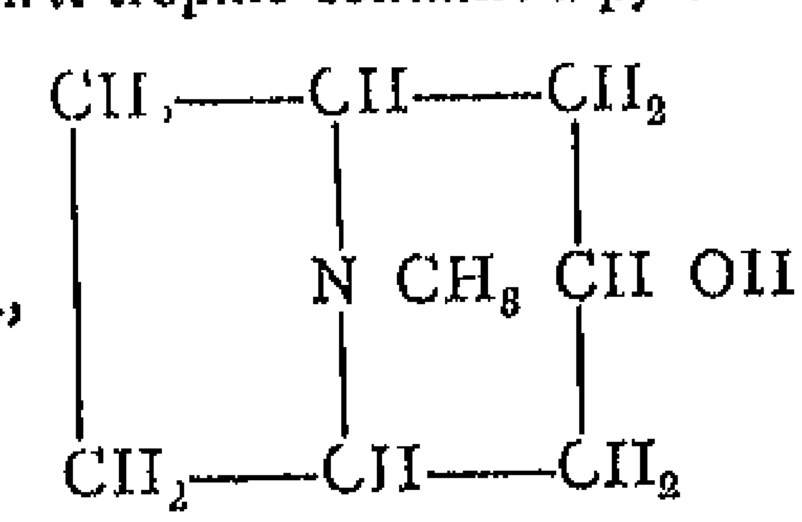
Nortropane, norhydrotropidine, $C_7H_{13}N$, is formed by distilling tropane in a stream of hydrochloric acid, when the N methyl group is removed as methyl chloride (Ladenburg)



Tropane hydrochloride — Nortropane

Nortropane is a transparent crystalline substance, boiling about 161° and melting about 60° *When distilled with zinc dust it yields 2 ethylpyridine*, a reaction which first led to the discovery that tropine contains a pyridine nucleus

Tropine, tropanol,



Tropine, the basic cleavage product of most of the Solanaceæ alkaloids (*e g* atropine), is one of the most important derivatives of

[1] *Ann*, 1901, **317**, 315

tropane It has been more completely investigated than any of the other derivatives, with results which gave the first insight into the structure of the tropane ring

Formation and Properties of Tropine

Tropine was first obtained by the hydrolysis of atropine with barium hydroxide (Kraut, 1863), and was later isolated in a similar manner from hyoscyamine (Ladenburg) and belladonnine (Merling) Willstatter prepared tropine by the reduction of tropinone,[1] and finally effected its synthesis

The base, which is optically inactive, crystallises from absolute ether in large plates, m p 63°, and b p 229° It dissolves readily in water and alcohol, giving solutions with a strong alkaline reaction

ψ-Tropine, described later, is a geometrical isomeride of tropine

Constitution of Tropine

A summary of the reactions from which the constitution of tropine has been deduced is given in the table on p 685 The chief points to be noted are the following —

Proof of the presence of an alcoholic hydroxyl group in tropine is based on the transformation of the latter into tropidine by simple removal of water Since tropine is a tertiary base, and thus contains no hydrogen attached to nitrogen, it must be the hydrogen of this hydroxyl group which is replaced by an acidic radical in the alkaloid atropine

That tropine contains a pyridine nucleus follows from the conversion of tropidine into dibromo-pyridine and α-ethyl-pyridine

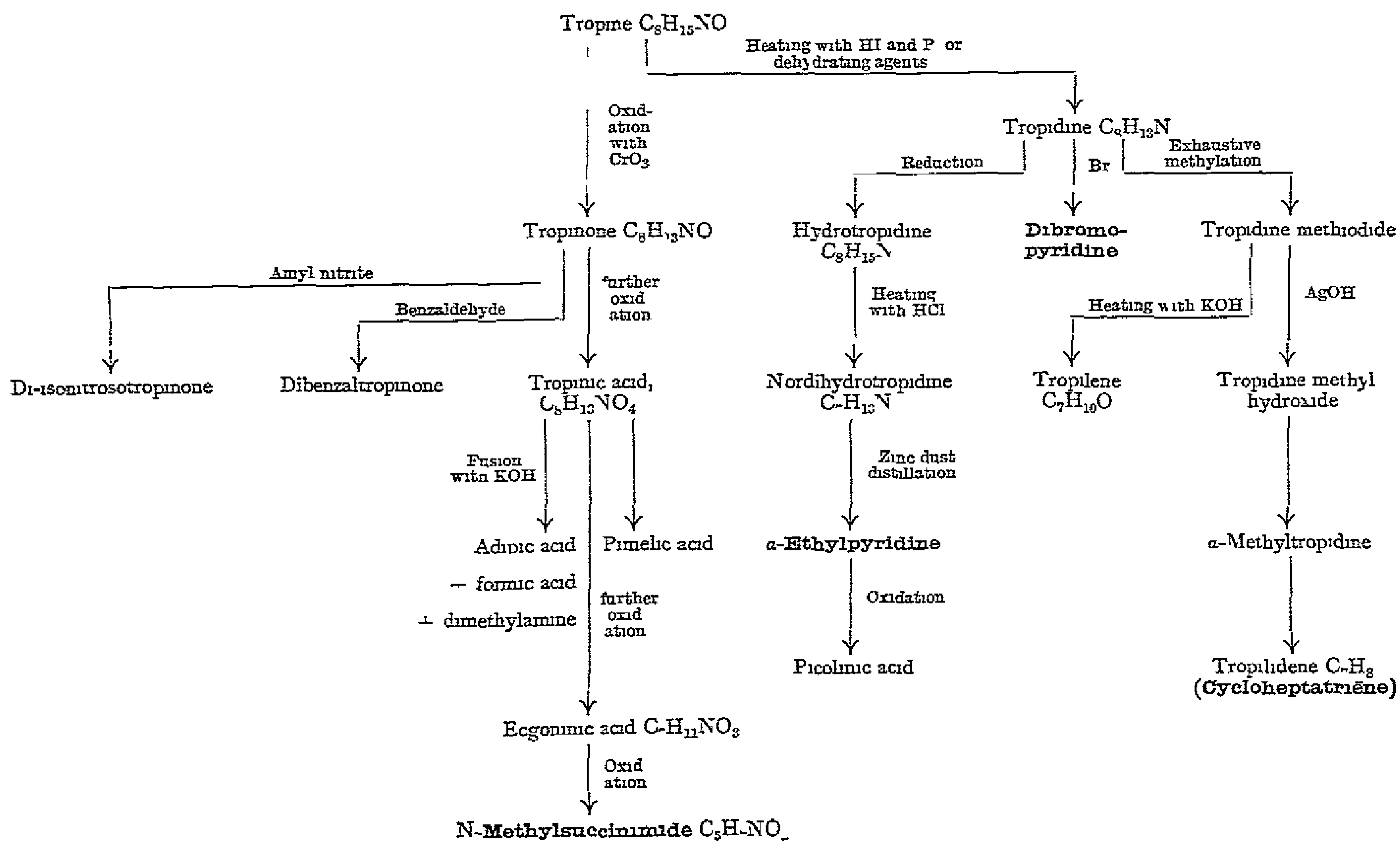
The presence of a seven-membered carbon ring in tropine is shown by the conversion of tropidine into tropilidene or cycloheptatriene on exhaustive methylation,[2] and also by the degradation of tropinic acid to normal pimelic acid[3] (see p 581)

Willstatter has conclusively proved the existence of a pyrrolidine nucleus in tropine by an examination of the degradation products formed on oxidation Tropinic acid was identified as 1-methyl-pyrrolidine-2-carboxylic-5-acetic acid, and by energetic oxidation was converted into N-methyl-succinimide (p 581) In this manner the pyrrolidine nucleus was isolated from tropine in a simple, well-known form

In establishing the above formula for tropine, a factor of prime importance was the observation that tropinone, the primary oxidation product of tropine, readily yields a dibenzal-compound and a di-isonitroso derivative, and must therefore contain the group $—CH_2\ CO\ CH_2—$, (see p 685)

[1] Willstatter and Iglauer, *Ber*, 1900, 33, 1170 [2] Merling, *Ber*, 1891, 24, 3110
[3] Willstatter, *Ber*, 1898, 31, 1534, 1542

Chief Reactions of Tropine



Synthesis of Tropine

Willstätter's synthesis of tropine is divided into two parts the synthesis of tropidine and its conversion into tropine

(a) *Synthesis of Tropidine*

This synthesis has been effected in two ways, only one of which is described here[1]

In the main this is a reversal of the stages by which tropine may be degraded to an unsaturated hydrocarbon containing a ring of seven carbon atoms The starting-point is suberone, obtained from suberic acid, and the synthesis proceeds in the following steps

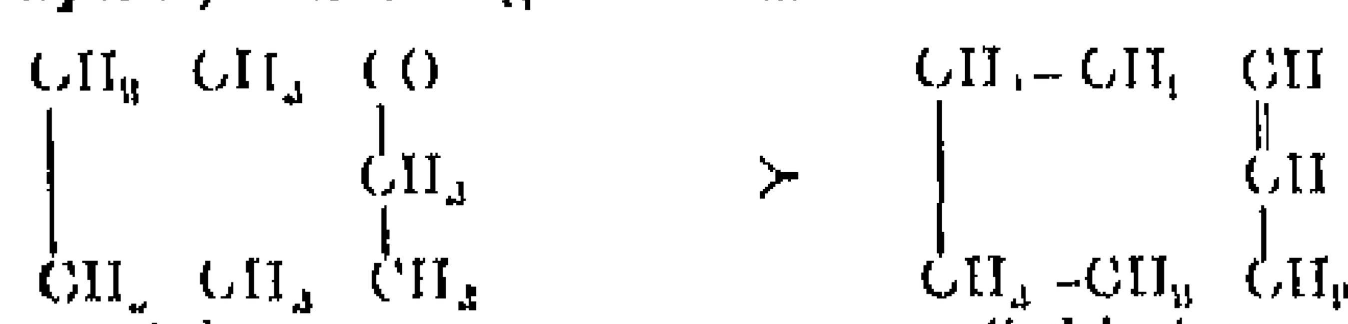
1 Suberone is converted into cycloheptene and thence into cycloheptadiene and cycloheptatriene

2 Cycloheptatriene is converted into dimethylamino cycloheptadiene, which is then reduced to dimethylamino cycloheptene

3 The hydrogen halide addition product of this monocyclic tropine base is transformed into a dicyclic tropane-methyl-ammonium salt, which on distillation yields tropidine

1 *Synthesis of Cycloheptatriene*

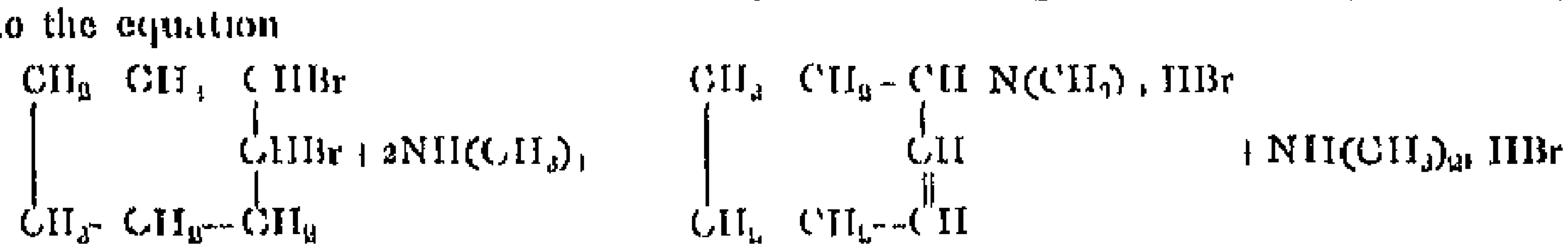
Suberic acid, which can be obtained from glutaric acid by the electrolytic method of Crum Brown and Walker, is converted into the calcium salt and distilled The *suberone*, or cycloheptanone, prepared in this way is first converted into the hydrocarbon *cycloheptene*, containing one double bond



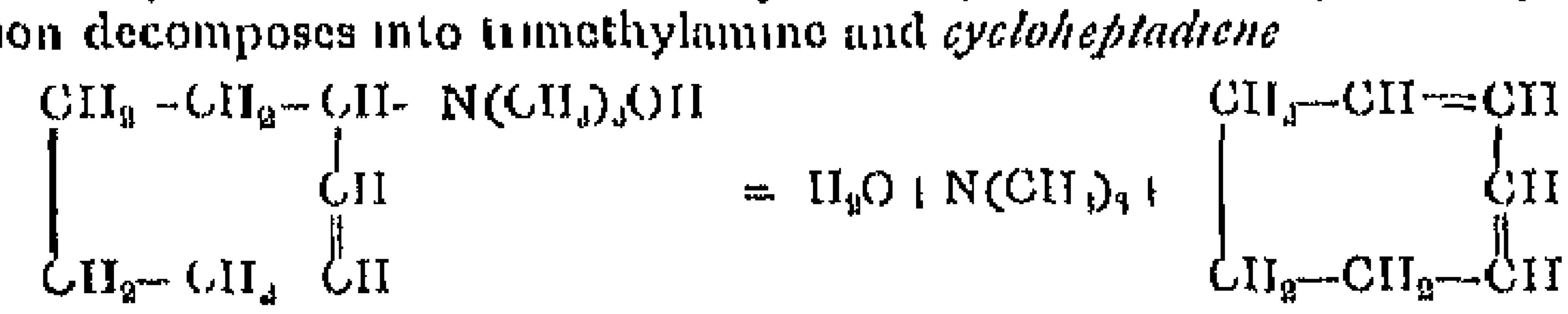
Suberone Cycloheptene

This can be accomplished either by treating suberyl iodide with alcoholic potash (Markownikoff), or by the exhaustive methylation of suberyl amine (amino cycloheptane) obtained by the reduction of suberone oxime (Willstätter)

A second double bond is introduced into the molecule by allowing cycloheptene dibromide, dissolved in indifferent solvents, to react with dimethylamine In this manner an unsaturated base Δ^2-*dimethylamino cycloheptene* is formed, according to the equation

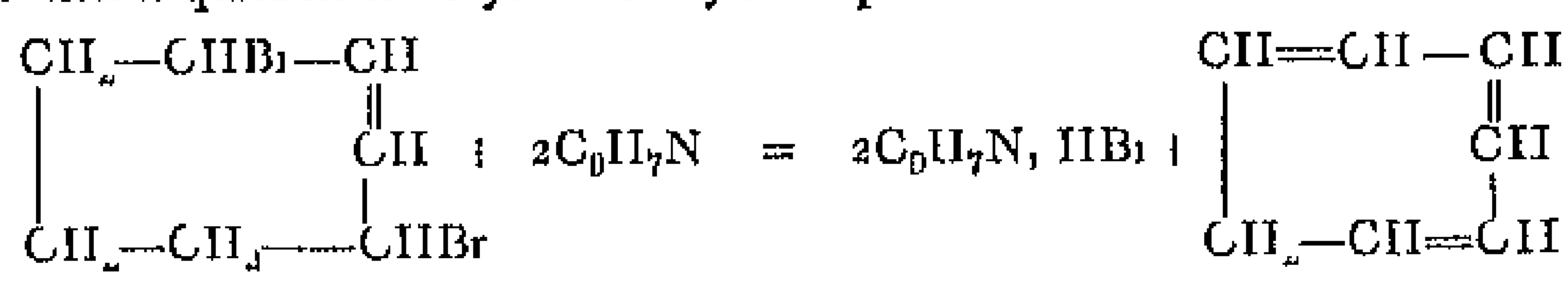


This base may be converted into the quaternary ammonium hydroxide, which on distillation decomposes into trimethylamine and *cycloheptadiene*



[1] Willstätter, *Ann*, 1901, **317**, 307

The dibromide of cycloheptadiene can be converted into cycloheptatriene by various methods When heated with quinoline, for example, hydrogen bromide is removed and a quantitative yield of cycloheptatriene is obtained

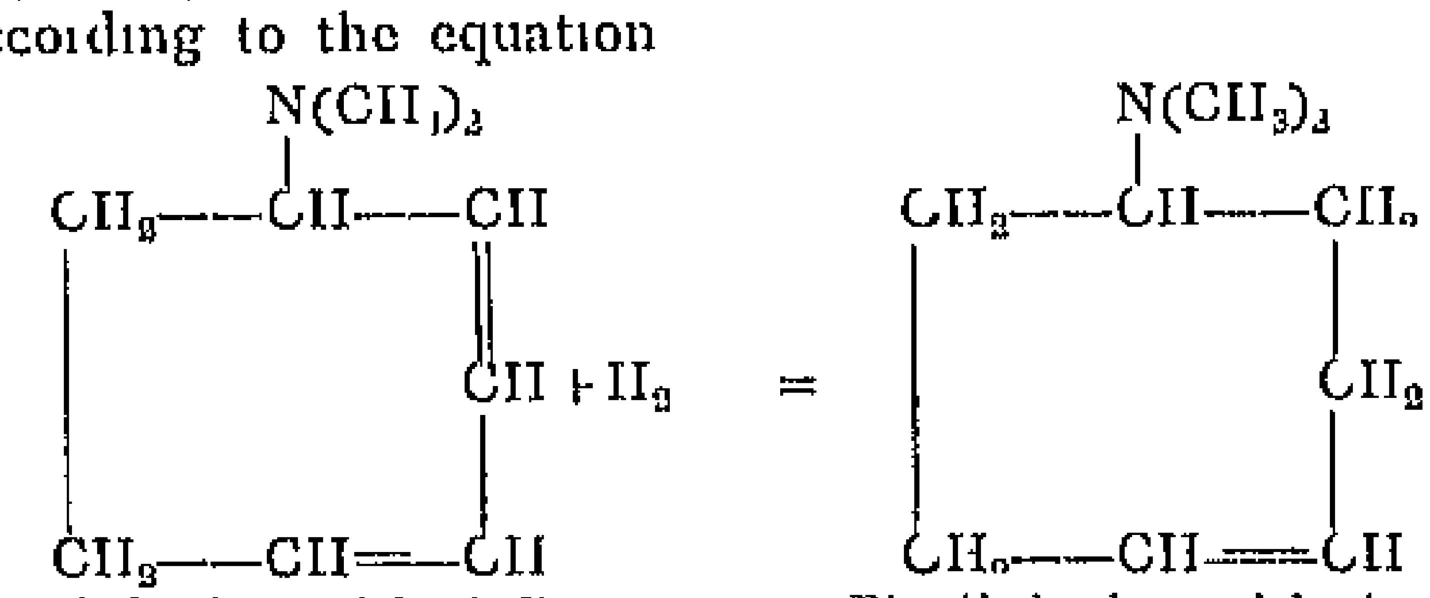


The synthetic cycloheptatriene produced in this way from suberone is identical in all respects with the tropilidene prepared from tropine

2 *Conversion of Cycloheptatriene into Tropidine*

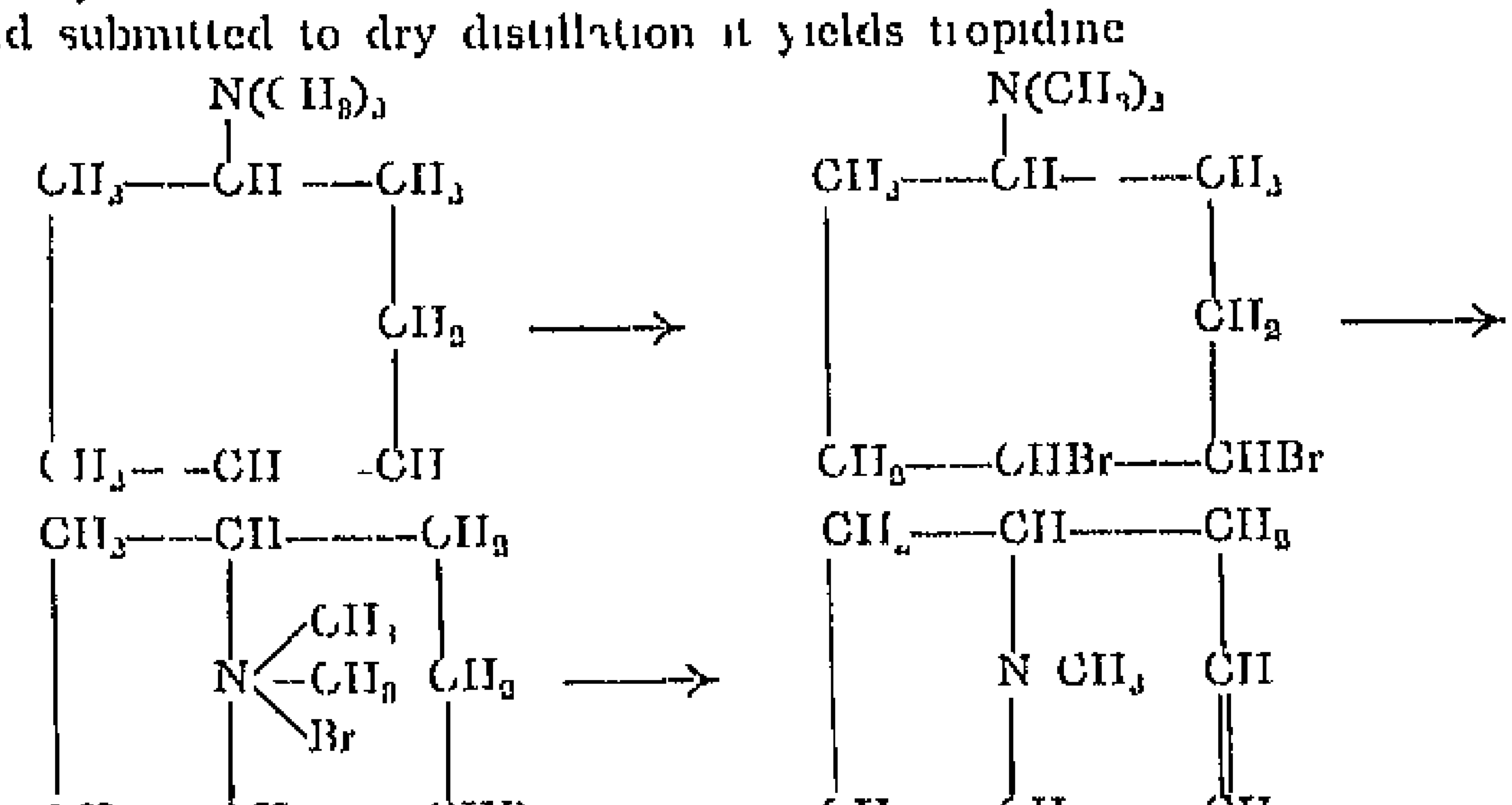
Cycloheptatriene hydrobromide, which is formed by treating the hydrocarbon in the cold with one molecular proportion of hydrogen bromide, reacts readily at ordinary temperatures with dimethylamine in benzene solution, with the production of *dimethylamino cycloheptadiene*

When the latter is reduced with sodium in alcoholic solution it passes into dimethylamino cycloheptene, the doubly unsaturated base taking up two atoms of hydrogen, according to the equation



Dimethylamino cycloheptadiene   Dimethylamino cycloheptene

Dimethylamino cycloheptene in acid solution adds on bromine to form a dibromide, which, on being warmed, rapidly undergoes rearrangement into 4 bromotropane methyl ammonium bromide Under the influence of alkali this substituted ammonium salt readily decomposes into hydrobromic acid and tropidine methyl ammonium bromide When the latter is converted into the chloride and submitted to dry distillation it yields tropidine



Tropidine

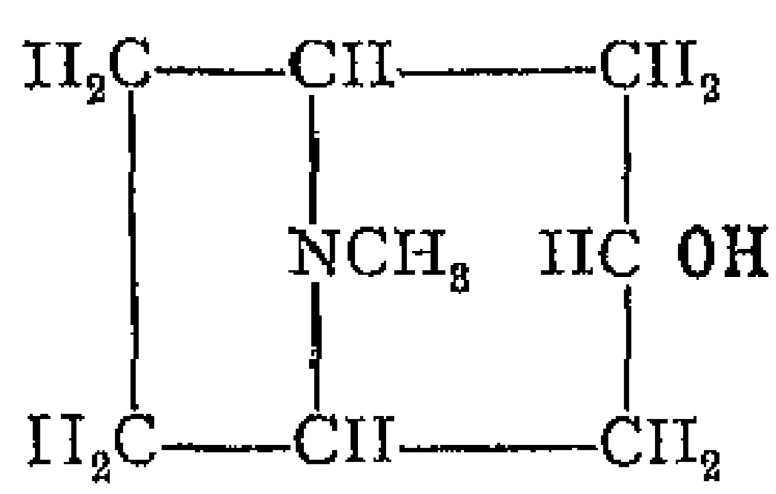
(b) *Conversion of Tropidine into Tropine*

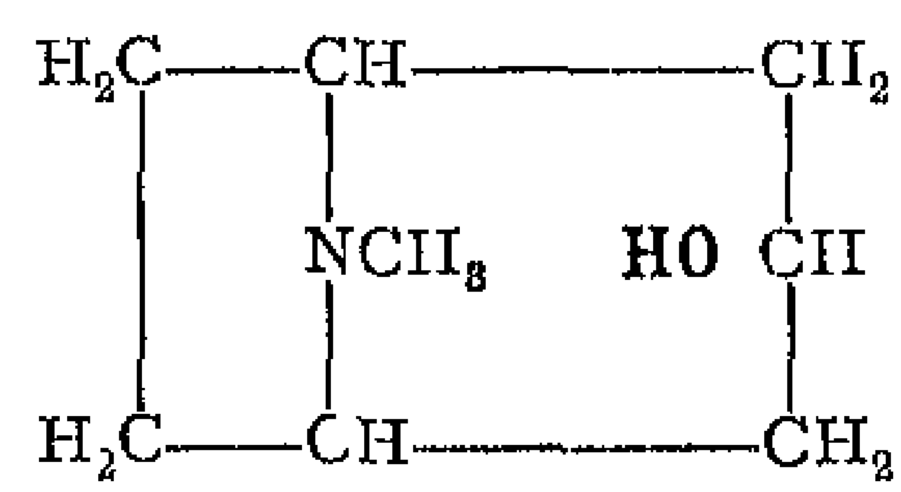
Tropidine may be converted into ψ-tropine by way of its hydrogen bromide addition compound, 3-*bromotropane* When this is heated

to 200° with sulphuric acid in a sealed tube it yields *ψ-tropine* (Willstätter).

Since ψ-tropine can be transformed into *tropine* (see below), the series of reactions just described constitutes a complete synthesis of tropine, and therefore also of the solanine alkaloids *atropine*, *atropamine*, *belladonnine*, and *hyoscyamine*, and the coca alkaloids *tropacocaine* and *r-cocaine*. This is treated in more detail under the individual alkaloids.

ψ-Tropine, pseudotropine, has the same constitution as its isomeride tropine, the relationship between these compounds being of the cis-trans type, similar to that existing between borneol and isoborneol (see p. 476 *et seq.*). Further examples of the same kind will be met with in the tropane series. The relationship may be illustrated by the following space formulæ:

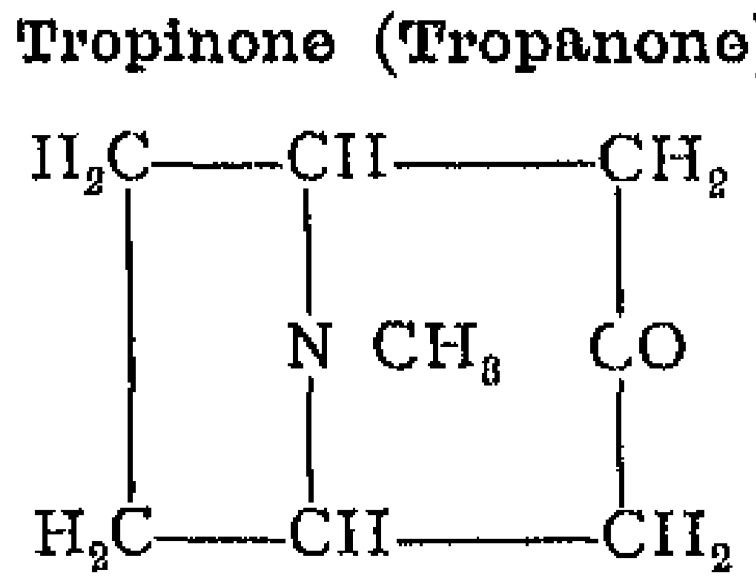




ψ-Tropine boils at 240° to 241°, and crystallises in needles of melting-point 108°. It is optically inactive, and readily dissolves in alcohol and water to give strongly alkaline solutions. The base can be identified and separated from tropine by means of its *picrate*,[1] $C_8H_{15}NO, C_6H_2(NO_2)_3OH$.

ψ-Tropine was discovered at a much later date than tropine and is less readily prepared. It can be obtained from the latter in two ways, viz., directly, by heating it with a solution of sodium ethoxide, and indirectly, by oxidation to tropinone and reduction with sodium and alcohol.[2] Conversely, ψ-tropine may be converted into tropine by oxidation to tropinone followed by reduction with zinc dust and hydriodic acid.[3] As already mentioned, the last reaction is a vital link in the synthesis of tropine and alkaloids derived from it.

Tropinone (Tropanone)



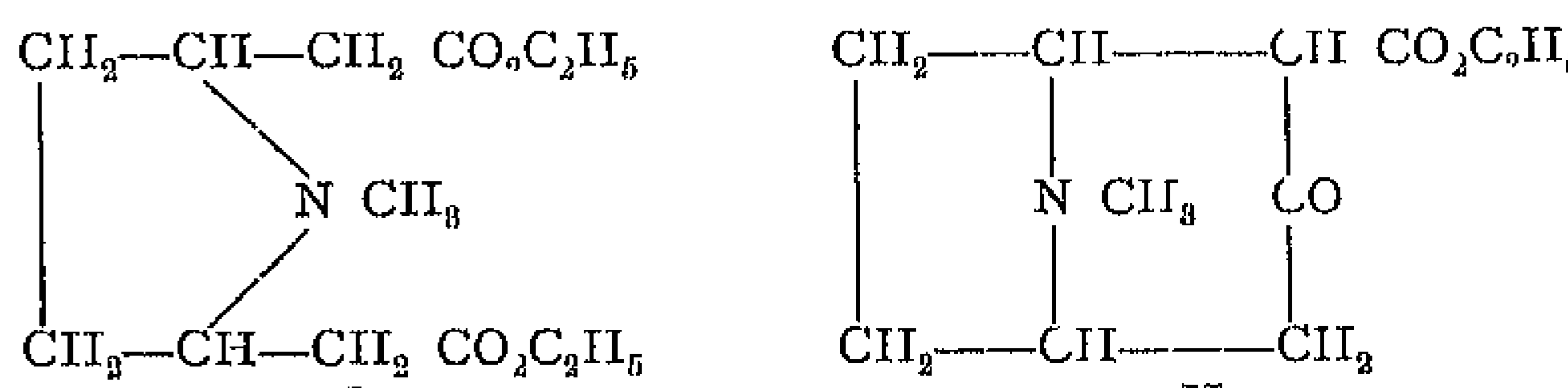
Tropinone is the ketone corresponding to the alcohol tropine.

[1] Willstätter, *Ann.* 1903, 326, 41. [2] Willstätter, *Ber.*, 1896, 29, 936. [3] *Ber.*, 1910, 43, 1170.

It was obtained simultaneously by Willstätter and by Ciamician and Silber by the oxidation of tropine with chromium trioxide in glacial acetic acid solution, and results in a similar manner from ψ-tropine and from ecgonine. On further oxidation it yields tropinic acid.

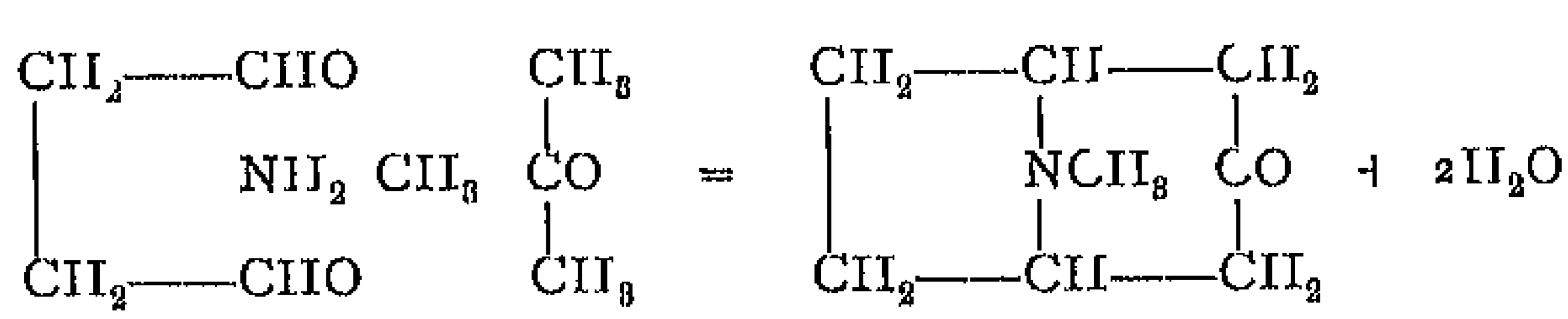
Tropinone melts at 41° to 42°, boils at 224° to 225°, and crystallises in long, flat needles. It is strongly basic, and displaces ammonia from ammonium salts. Its vapour forms white fumes with hydrochloric acid gas.

The following *synthesis of tropinone* was carried out by Willstätter.[1] N-Methylpyrrole-2 : 5-diacetic ester is reduced with hydrogen in presence of oxygenated platinum black to give N-methylpyrrolidine-2 : 5-diacetic ester[2] (I). The latter with sodium ethoxide undergoes intramolecular acetoacetic ester condensation to form tropinone carboxylic ester (II), which on warming with dilute mineral acids gives tropinone.

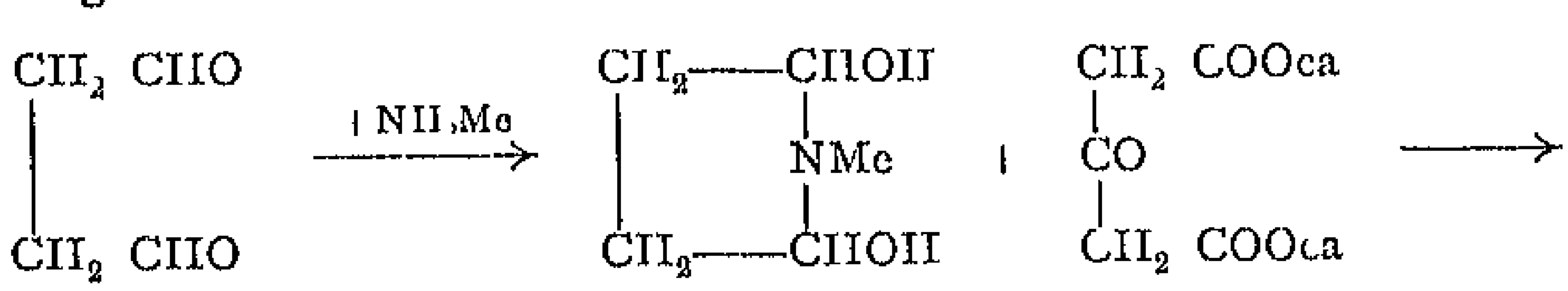


I II

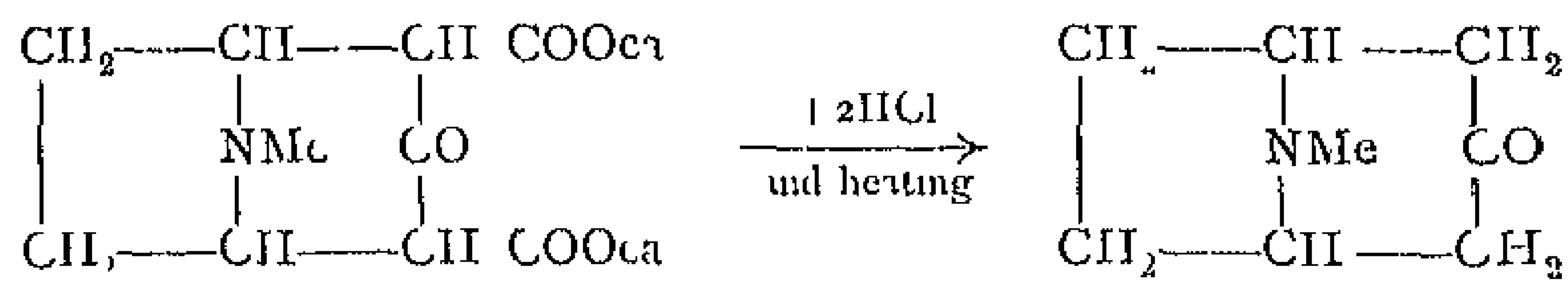
A remarkably simple synthesis of tropinone has recently been devised by Robinson.[3] Succindialdehyde—prepared from succindialdoxime and nitrous fumes—was allowed to interact in aqueous solution with acetone and methylamine. After the lapse of half an hour at the ordinary temperature tropinone was found to be present.



In an experiment in which the calcium salt of acetone dicarboxylic acid was employed in place of acetone, a yield of tropinone amounting to 42 per cent of the theory was obtained. The tropinone dicarboxylate first formed readily parts with two molecules of carbon dioxide on being heated in acid solution.



[1] Willstätter and Bommer, *Ann.*, 1921, 422, 15. [2] Willstätter and Jaquet, *Ber.*, 1918, 51, 767. [3] Robinson, *J. C. S.*, 1917, 111, 762.



On the ease with which these reactions proceed, Robinson has based a theory of the mechanism of the phytochemical synthesis of certain alkaloids in plants[1]

Mention has already been made of the existence of a number of derivatives of tropinone which point to the latter containing the group CH_2 CO CH_2 (see pp 684 and 685) These cannot be described further, but from their occurrence it followed that tropine contained the group CH_2 CHOH CH_2, and also, when other facts were taken into account, a pyrrolidine ring Hence Willstätter's investigations on tropinone derivatives had an important bearing on the constitution of tropine, as well as on that of atropine, cocaine and other alkaloids

Behaviour of Tropinone on Reduction[2]—The best results were obtained by reducing tropinone in the cold with zinc dust and hydriodic acid (sp gr 1 7 to 1 96) In this way a good yield of tropine, together with a smaller amount of ψ-tropine, was isolated Since tropinone can be obtained by the oxidation of ψ tropine, it is thus possible to pass from ψ-tropine through tropinone into tropine, a change which cannot be effected in any other manner, and which has been of value in connection with the synthesis of tropine, atropine and other compounds

Tropinone has also been obtained by the oxidation of ecgonine, a hydrolysis product of cocaine and tropacocaine The reduction of the ketone to tropine therefore makes it possible to convert tropacocaine or cocaine into atropine

Cocaine ⟶ ecgonine ⟶ tropinone ⟶ tropine ⟶ atropine

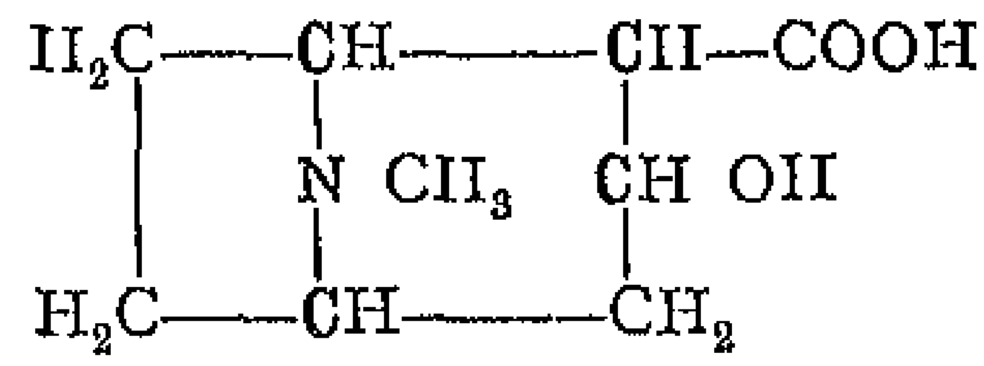
It should be mentioned, however, that the relationship between cocaine and atropine had been shown much earlier by Einhorn, by the conversion of anhydro ecgonine into tropidine (see anhydro-ecgonine)

The reduction of tropinone with zinc dust and hydriodic acid, even at very low temperatures, proceeds beyond the formation of the alcohol base and finally yields tropane

When reduced with sodium in moist ethereal or in alcoholic solution, tropinone is converted into ψ-tropine, the same result being obtained by use of sodium amalgam in weakly acid solution[3]

[1] *S*, 1917, 111, 876 [2] Willstätter and Iglauer, *Ber*, 1900, 33, 1172 *Ann*, 1903,
[3] Willstätter, *Ber*, 1896, 29, 936

Ecgonines, 3-Hydroxytropane-2-Carboxylic Acids



Ecgonine, as will be seen above, contains four asymmetric carbon atoms and should therefore exist in 16 optically active forms. As, however, the $—CH_2.CH_2—$ bridge united to the piperidine ring can only be attached in the *cis*-position, the number of possibilities is reduced to 8. So far only two of these are known, viz., ordinary *l*-ecgonine and the *d*-ecgonine (*d*-pseudoecgonine) produced from it by the action of alkali. To these must be added synthetic, optically inactive *i*-ecgonine. The *l*- and *d*-ecgonines already known are not optical antipodes, but possess specific rotations of different magnitudes. If we recall the behaviour of inactive tropine and *ψ*-tropine towards alkalis, it seems highly probable that *l*-ecgonine corresponds to the alkali-labile tropine, and *d*-ecgonine to the alkali-stable geometrical isomeride *ψ*-tropine. The structural difference probably depends on the relative positions of the hydroxyl and N-methyl groups. In accordance with a proposal of Willstätter,[1] it might be more satisfactory to extend the above nomenclature by describing dextrorotatory ecgonine as *d*-*ψ*-ecgonine, in distinction to ordinary or *l*-ecgonine, or, in general, by dividing the ecgonines and the cocaines derived from them into the ecgonine series and the pseudoecgonine series, according to the orientation of the hydroxyl group.

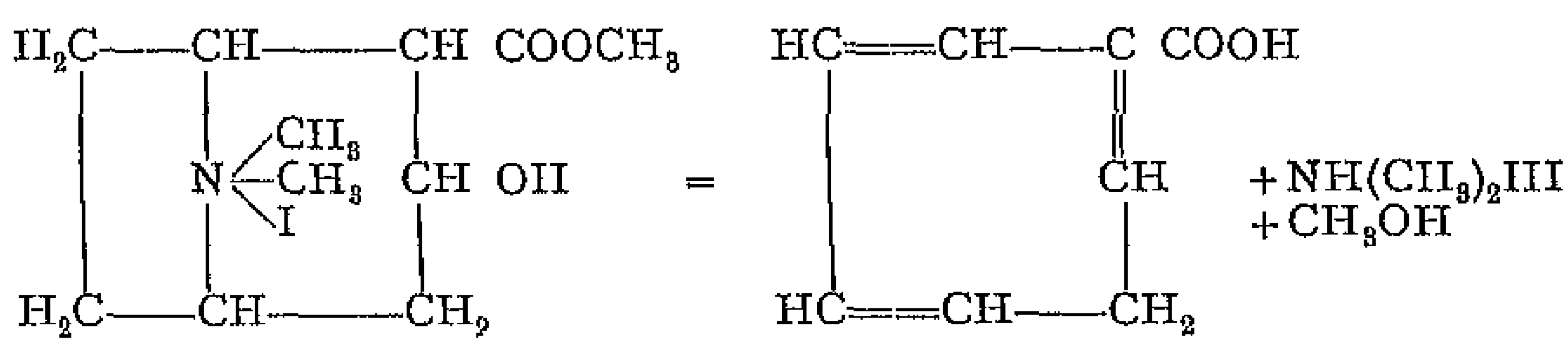
***l*-Ecgonine**, $C_9H_{15}NO_3+H_2O$, is the more interesting of the optically isomeric ecgonines, since from it is derived the important alkaloid *l*-cocaine (methyl ester of benzoyl-ecgonine).

Constitution of Ecgonine.—The presence of a pyridine ring in ecgonine was established by Stoehr, who obtained *α*-ethyl-pyridine by distilling the alkaloid with zinc dust. The structural similarity between tropine and ecgonine, *i.e.*, their derivation from the same parent substance, followed from Einhorn's discovery that when anhydroecgonine is heated to 280° with hydrochloric acid it decomposes into carbon dioxide and tropidine (p. 694). This result was also deduced from the researches of Liebermann, who converted ecgonine by oxidation with chromic acid into *d*-tropinic acid and ecgoninic acid. In this reaction tropinone occurs as an intermediate product. The varying opinions as to the constitution of tropine have therefore also had their reflections on that of ecgonine. Definite proof that the hydroxyl group occupies the same position in ecgonine as in tropine, and that the carboxyl group is attached to a neighbouring carbon

[1] *Ann.*, 1903, 326, 47.

atom, as indicated in the above formula, was supplied by the work of Willstätter and Müller[1] It was found that on gentle oxidation with chromic acid ecgonine could be converted into tropinone, *i e*, into the ketone which is the primary oxidation product of tropine and ψ-tropine, and further, that the behaviour of ecgonine was not that of an α- or γ-hydroxy acid Hence the carboxyl and hydroxyl groups must occupy the β-position to one another, and ecgonine is therefore a β-carboxylic acid of tropine Its degradation to N-methylsuccinimide has already been described on p 581

When warmed with alkalis, the methiodides of *l*-, *d*- and *r*-ecgonine esters break down into β-cycloheptatriene-carboxylic acid, as follows —



Ecgonine possesses the properties of an amino acid, forming salts with both bases and acids The presence of the carboxyl group is not shown by any acid reaction, but is revealed in the stability of the alkali salts towards carbon dioxide, and the production of esters on treatment with alcohols and hydrogen chloride The alcoholic hydroxyl group may be detected by the formation of esters on treatment with acid chlorides and anhydrides, and in the ease with which the compound parts with water and passes into anhydro-ecgonine (ecgonidine)

Preparation of l-*Ecgonine* —*l*-Ecgonine is obtained by hydrolysing *l*-cocaine with hydrochloric acid, dilute sulphuric acid, or barium hydroxide Similarly, the uncrystallisable mixture of partly amorphous bases, obtained in quantity as a by-product in the isolation of cocaine from coca leaves, also yields *l*-ecgonine on hydrolysis

The preparation of ecgonine from cocaine residues is of value in the technical production of cocaine, since ecgonine can readily be converted into cocaine

l-Ecgonine crystallises in monoclinic hemimorphic prisms (+1 mol H_2O), which become anhydrous at 120° and melt with decomposition at 198°

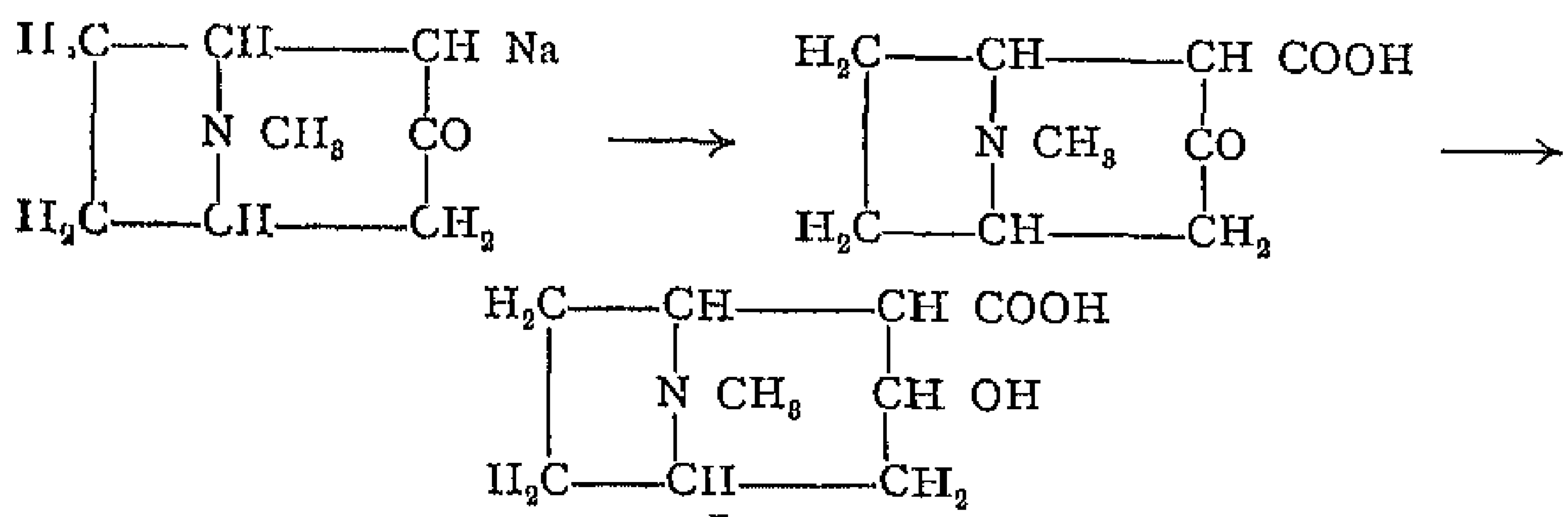
d-**Ecgonine**, (*d*-ψ-ecgonine), was first obtained by Einhorn by warming ordinary *l*-ecgonine with concentrated alkali It also results from the treatment of cocaine, benzoyl ecgonine, or the alkaloids accompanying cocaine with caustic potash, when the *l* ecgonine first formed undergoes molecular rearrangement Lieber-

[1] *Ber*, 1898, 31, 2655

mann and Giesel obtained it as a fission product of the *d*-cocaine discovered by them among the coca alkaloids It forms monoclinic prisms or plates of melting-point 264°

r-**Ecgonine**, the racemic compound, was prepared synthetically by Willstätter[1] in the following manner, thus completing the synthesis of cocaine

Sodium tropinone, suspended in ether, unites with carbon dioxide at room temperature to give sodium tropinone-carboxylate This compound can be obtained more readily by the simultaneous action of sodium and carbon dioxide on the amino-ketone When the crude tropinone-carboxylate is reduced in cold, faintly acid solution with sodium amalgam it yields a mixture of two isomeric compounds, having the composition of ecgonine but of different constitutions, viz, ψ-tropine-O-carboxylic acid and *r*-ecgonine Only the latter is of interest in this connection, and its formation is probably due to part of the sodium tropinone reacting as the ketonic salt (*cf* aceto-acetic ester) and thus yielding tropinone β-carboxylic acid, which on reduction passes into *r*-ecgonine, as shown below —



Ecgonine

A further synthesis of *r*-ecgonine was carried out by Willstatter[2] in connection with the synthesis of tropinone described on p 689, tropinone-carboxylic ester being converted by reducing agents into the ester of *r*-ecgonine

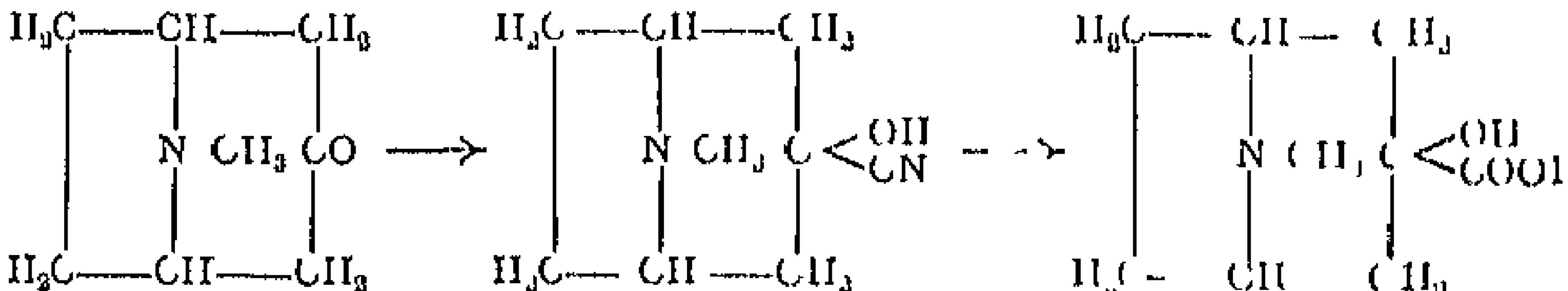
r-Ecgonine contains four asymmetric carbon atoms and is not affected by heating with alkalis It crystallises with 3 mols H_2O and melts with decomposition at 251°

α-Ecgonine, 3-Hydroxytropane-3-Carboxylic Acid

Before the constitution of *l*-ecgonine was known in detail, an attempt had been made to synthesise the racemic compound from tropinone As a ketone, the latter unites with hydrogen cyanide to form *tropinone cyanhydrin* This on hydrolysis yields a compound of the composition of ecgonine, from which it differs in having

[1] Willstatter and Bode, *Ann*, 1903, 326, 47 [2] Willstätter and Bommer, *Ann*, 1921, 422, 15

the carboxyl and hydroxyl groups both attached to the same carbon atom. For this structural isomeride of ecgonine Willstätter proposed the name α-ecgonine.



Tropinone — Tropinone cyanhydrin — α-Ecgonine

On benzoylation, the methyl ester of α-ecgonine is converted into α-cocaine (see p. 700). The only interest of these α-compounds lies in the part they have played in furthering our knowledge of the constitution of ecgonine. Since α-ecgonine was not identical with ordinary ecgonine, it followed that the carboxyl group in the latter could not occupy the α-position.

In chemical behaviour α-ecgonine and its derivatives differ markedly from ordinary ecgonine. Whereas the methiodides of the ecgonine group, being β-betaines, are easily decomposed by alkalis, those of the α-ecgonine group, being γ-betaines, exhibit great stability.

Tropidine (Tropene)

Tropidine (formula, see p. 687) has been mentioned frequently in the foregoing pages. It was first prepared from tropine by heating it to 180° with fuming hydrochloric acid and glacial acetic acid, or with sulphuric acid (Ladenburg). According to Einhorn, it is also formed by heating anhydro-ecgonine (tropene-2-carboxylic acid) with concentrated hydrochloric acid to 280°, when carbon dioxide is eliminated:

$$\underset{\text{Anhydro-ecgonine}}{C_8H_{12}(CO_2H)N} = CO_2 + \underset{\text{Tropidine}}{C_8H_{13}N}$$

Tropidine is further formed by heating ψ-tropine with glacial acetic acid containing hydrochloric or sulphuric acid.

Cocaine ⟶ *ecgonine* ⟶ *anhydro-ecgonine* ↘

Atropine ⟶ *tropine* ⇄ *tropidine*

The *syntheses of tropidine* carried out by Willstätter have already been described. These are of great importance, since tropidine may be converted through ψ-tropine into tropine (see pp. 687, 688), and also into *r*-ecgonine. In this manner several alkaloids of the tropane series, particularly atropine, are accessible from the synthetic side.

Properties of Tropidine.—Tropidine is a liquid base with a stupefying odour like that of conine. It boils at 162° to 163° (corr.) and is less soluble in hot water than in cold. The aqueous solution turns litmus paper blue.

When treated with excess of bromine at 170° to 180°, tropidine yields ethylene dibromide and dibromo-pyridine (Ladenburg, 1883).

On exhaustive methylation tropidine first gives *α-methyltropidine*, and finally, by distillation of α-methyltropidine-methylammonium hydroxide, it yields *tropilidene* or *cycloheptatriene*[1] (see p 687)

$$C_7H_9 \cdot N(CH_3)_3OH = C_7H_8 + N(CH_3)_3 + H_2O$$

Alkaloids of the Tropane Series

To this group belong the alkaloids of the Solanaceæ and the coca alkaloids

1 ALKALOIDS OF THE SOLANACEÆ

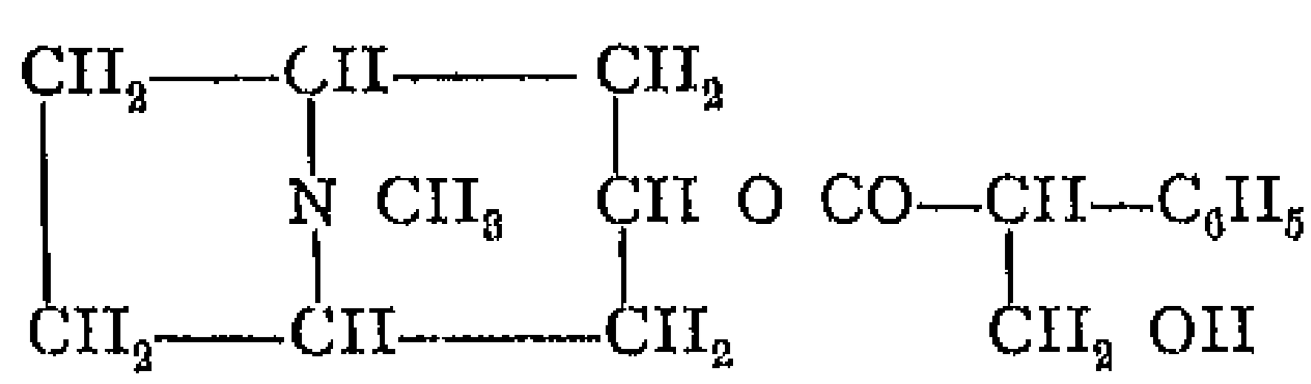
In many members of the Solanum family, such as *Atropa belladonna* (Deadly Nightshade), *Datura stramonium* (Thorn apple), *Hyocyamus niger* (Henbane), are found a number of alkaloids closely related to one another in their properties and chemical constitution Chief among these are two isomerides of the composition $C_{17}H_{23}NO_3$, viz, optically inactive *atropine* and laevorotatory *hyoscyamine*

Atropine is actually the racemic modification of hyoscyamine

Accompanying the above are found the following less completely investigated Solanum bases

Atropamine	$C_{17}H_{21}NO_2$
Belladonnine	$C_{17}H_{21}NO_2$
Hyoscine or scopolamine	$C_{17}H_{21}NO_4$

Atropine, tropine ester of *dl*-tropic acid



This base occurs in the Deadly Nightshade (*Atropa belladonna*), in *Datura stramonium*, and in the root of *Scopolia japonica*

According to Mein, 1000 parts of dried belladonna root contain about 3 3 parts of atropine, which is isolated by extraction with alcohol

Atropine is optically inactive and crystallises from alcohol and chloroform in prisms, m p 115° to 116° It has a sharp and bitter taste and is a strong poison Owing to its property of dilating the pupil of the eye (mydriasis) it is extensively employed in medicine By its use it is possible to counteract the stoppage of the heart caused by muscarine

Inactive atropine results from the racemisation of its stereoisomeride hyoscyamine, (1) when the latter is heated to 110° in absence of air, (2) on being treated in alcoholic solution with a few drops of alkali, or (3) spontaneously in the course of time

When treated with nitric acid, and also when warmed with acetic

[1] Merling, *Ber*, 1891, 24, 3109 Willstätter, *Ber*, 1898, 31, 1534

or benzoic anhydride, or phosphorus pentoxide, atropine loses a molecule of water and yields *apoatropine*, $C_{17}H_{21}NO_2$, which has been found to be identical with the naturally occurring *atropamine*. The latter crystallises in prisms, m.p. 60° to 62°, and does not induce mydriasis. If atropine is heated to 130°, it loses water in another manner and a certain proportion is converted into *belladonnine*, an uncrystallisable mass with the appearance of varnish.

Atropine salts have only a low power of crystallisation. Atropine sulphate $(C_{17}H_{23}NO_3)_2H_2SO_4+H_2O$, which is employed in eye surgery, is obtained in crystalline condition by dropping sulphuric acid dissolved in absolute alcohol (1 : 10) into atropine (10 parts) in dry ethereal solution. The sulphate separates in the form of needles.

Constitution and Synthesis of Atropine

In 1863 Kraut discovered that atropine, on being boiled with aqueous baryta, decomposed into *tropine* and *atropic acid*.

A year later it was shown by Lossen that the primary product of decomposition was not atropic acid, $C_9H_8O_2$, but *tropic acid*, $C_9H_{10}O_3$, and that the latter was then converted into the former by loss of 1 mol. water. Consequently the change undergone by atropine is merely the hydrolysis of an ester into acid and (basic) alcohol:

$$\underset{\text{Atropine}}{C_{17}H_{23}NO_3} + H_2O = \underset{\text{Tropine}}{C_8H_{15}NO} + \underset{\text{Tropic acid}}{C_9H_{10}O_3}$$

By reversing the above process Ladenburg,[1] in 1879, effected a partial synthesis of atropine. On treating tropine tropate with hydrochloric acid he succeeded in regenerating atropine, thus proving it to be the tropine ester of tropic acid.

The problem of the constitution of atropine therefore resolved itself into two parts: the study of tropic acid and that of tropine.

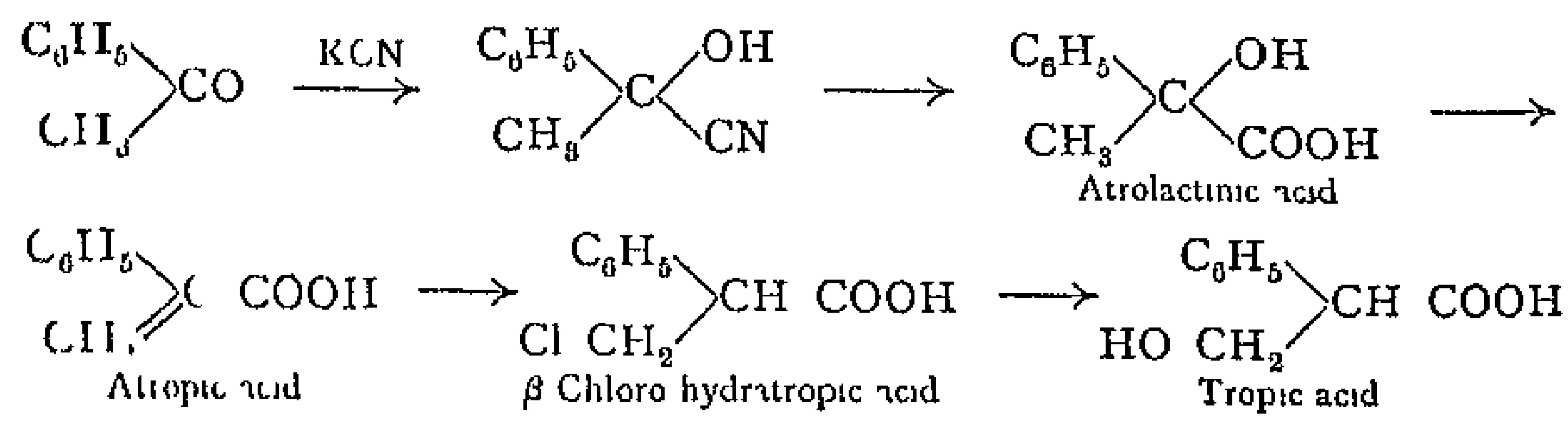
The structure of tropic acid was soon cleared up and the compound synthesised by Ladenburg and Rugheimer.[2] It is, however, more readily prepared by the synthesis of E. Muller, in which phenylacetic ester, $C_6H_5 \cdot CH_2 \cdot COOC_2H_5$, is condensed with formic acid to give *formyl-phenylacetic ester*. This on reduction with aluminium amalgam yields *tropic ester*:[3]

$$C_6H_5 \cdot CH\left\langle\begin{matrix} CH \cdot O \\ COOC_2H_5 \end{matrix}\right. \longrightarrow C_6H_5 \cdot CH\left\langle\begin{matrix} CH_2OH \\ COOC_2H_5 \end{matrix}\right.$$

Another method of preparing this important acid is that due to McKenzie and Wood.[4] Acetophenone is converted into atrolactinic

[1] *Ber.*, 1879, **12**, 941; **13**, 104. *Ann.*, 1883, **217**, 78. Wolffenstein and Mamlock, *Ber.*, 1908, **41**, 723. [2] *Ber.*, 1880, **13**, 373. Spiegel, *Ber.*, 1881, **14**, 236. Kraut and Merling, *Ber.*, 1881, **14**, 330. *Ann.*, 1881, **209**, 3. [3] E. Muller, *Ber.*, 1918, **51**, 252. W. Wislicenus and Bilhuber, *ibid.*, 1237. [4] McKenzie and Wood, *J. C. S.*, 1919, **115**, 830.

acid, which on being heated under diminished pressure gives atropic acid. The latter unites with HCl in ethereal solution to form β-chlorohydratropic acid, which finally yields tropic acid on being boiled with aqueous sodium carbonate.



The presence of an asymmetric carbon atom in tropic acid indicated the possibility of resolving the acid into its active components, and thus of preparing optically active atropines. The resolution of tropic acid was effected by Ladenburg by means of the quinine salt, and from the active components the *active atropines* were then built up. By using other acids in place of tropic acid Ladenburg prepared other esters of tropine, to which he gave the collective name of *tropeines*. These artificial alkaloids are described below.

It was not until much later that the structure of the alcohol tropine, the remaining hydrolysis product of atropine, was successfully elucidated and its synthesis accomplished. This has been described in detail on p. 686 *et seq.*

Hence the complete **synthesis of atropine** involves the following stages:—1. Synthesis of glycerol. 2. Glycerol into glutaric acid. 3. Glutaric acid into suberone. 4. Suberone into tropidine. 5. Tropidine into tropine. 6. Synthesis of tropic acid. 7. Atropine from tropine and tropic acid.

For the *relationship between atropine and cocaine*, see pp. 686 to 695.

Homatropine or *phenyl-glycolyl-tropeine*, $C_{16}H_{21}NO_3$, is by virtue of its physiological action the most important compound of the tropeine group after atropine and hyoscyamine. It is prepared from tropine and mandelic acid, and crystallises from absolute ether in transparent prisms, which are deliquescent and melt at 95.5° to 98.5°. *Homatropine hydrobromide*, $C_{16}H_{21}NO_3,HBr$, crystallises in rhombic plates and is only moderately soluble in cold water.

In the form of its hydrobromide, homatropine possesses almost as powerful an action in dilating the pupil of the eye as atropine, but the effect disappears comparatively rapidly. It behaves similarly with respect to the paralysis of the power of accommodation. Homatropine is a much weaker poison than atropine and is also used in eye surgery.[1]

[1] Ladenburg, *Ann.*, 1883, **217**, 82. Jowett and Pyman, *J. C. S.*, 1909, **95**, 1090.

According to the investigations of Ladenburg and Volkers the mydriatic power of the tropeines is not solely dependent on the presence of the tropine residue in the molecule, it is also necessary for the latter to be united to an acid containing an alcoholic hydroxyl grouping [1] Some exceptions to this statement are known

Hyoscyamine, *l-Tropic Ester of Tropine*

Hyoscyamine was first prepared from henbane, and occurs also in a number of other plants It has been found by Dunstan and Brown [2] in *Hyoscyamus muticus*, and by Thoms and Wentzel [3] in mandragora root

It crystallises from alcohol in needles, m p 108 5°, and resembles atropine in its sharp, penetrating taste and mydriatic action The main difference between these two alkaloids lies in the laevorotation of hyoscyamine as compared with the optical inactivity of atropine

The conversion of hyoscyamine into atropine (racemisation) may be effected by fusion, or by the addition of a small amount of alkali to an alcoholic solution of the compound It has also been found that the change takes place slowly, without appreciable hydrolysis, when hyoscyamine is allowed to stand in alcoholic solution,[4] and is accelerated by the addition of tropine Since hyoscyamine undergoes hydrolysis in aqueous solution, even at the ordinary temperature, to form *l*-tropic acid and inactive tropine, it follows that the conversion of hyoscyamine into atropine is due to alteration of the tropic acid component This change is now known to be due to racemisation, the racemic nature of the inactive tropic acid from atropine having been established by resolution

Additional proof that the isomerism of atropine and hyoscyamine depends solely on the inactivity or activity of the tropic acid residue has been supplied by the conversion of atropine into *d*- and *l*-hyoscyamines This was first effected by hydrolysing commercial atropine into tropine and tropic acid, resolving the latter, and uniting the *d*- and *l*-tropic acids separately with tropine to give *d*- and *l*-hyoscyamines [5] Barrowcliff and Tutin [6] also resolved atropine directly, by use of *d*-camphor-sulphonic acid

Hyoscyamine can therefore be synthesised by stages similar to those used in the case of atropine (p. 697), the final combination being with *l*-tropic acid in place of the racemic compound

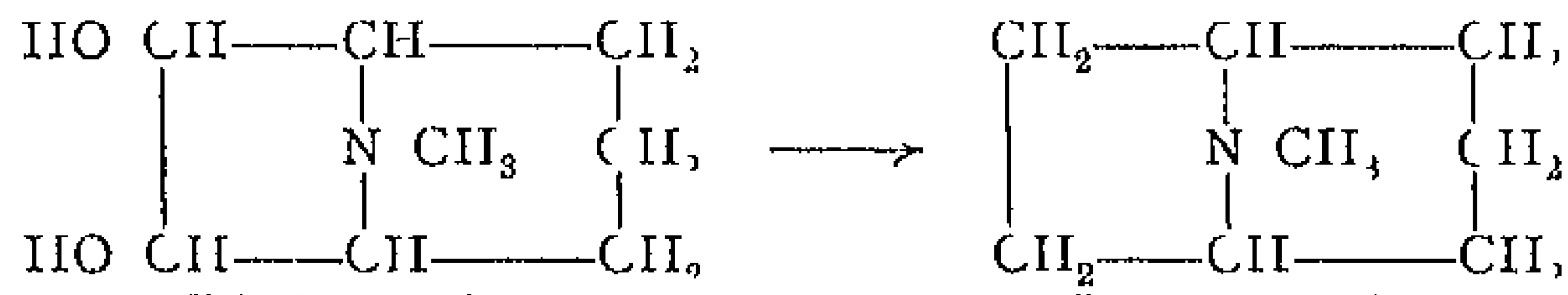
Dehydrating agents convert hyoscyamine into *atropamine* and *belladonnine* These alkaloids are also obtained in the same way from atropine (see p 696)

The optically isomeric alkaloids **hyoscine** and **scopolamine**, $C_{17}H_{21}NO_4$, are also found in plants of the Solanaceae family Scopolamine (m p of monohydrate, 59°) is laevorotatory, and with alkalis is readily racemised to hyoscine On hydrolysis scopolamine yields tropic acid and *scopoline*, but it is not the scopoline ester of tropic acid. Recent work by Hess and Wahl [7] points to the alkaloid being the tropic ester of a symmetrical base which is isomeric with scopoline, and into which it isomerises during the process of hydrolysis

Scopoline, $C_8H_{13}NO_2$, strongly resembles tropine, $C_8H_{15}NO$, in its

[1] Compare also J v Braun, O Braunsdorff and K Räth, *Ber*, 1922, 55, 1666 [2] *J C S*, 1899, 75, 72 [3] *Ber*, 1898, 31, 2031 [4] Gadamer, *J C S*, 1901, 80, A, i, 605 [5] Amenomiya, *J C S*, 1903, 84, A, i, 109 [6] Barrowcliff and Tutin, *J C S*, 1909, 95, 1966 [7] K Hess and Wahl, *Ber*, 1922, 55, 1979 Willstätter and Berner, *Ber*, 1923, 56, 1079

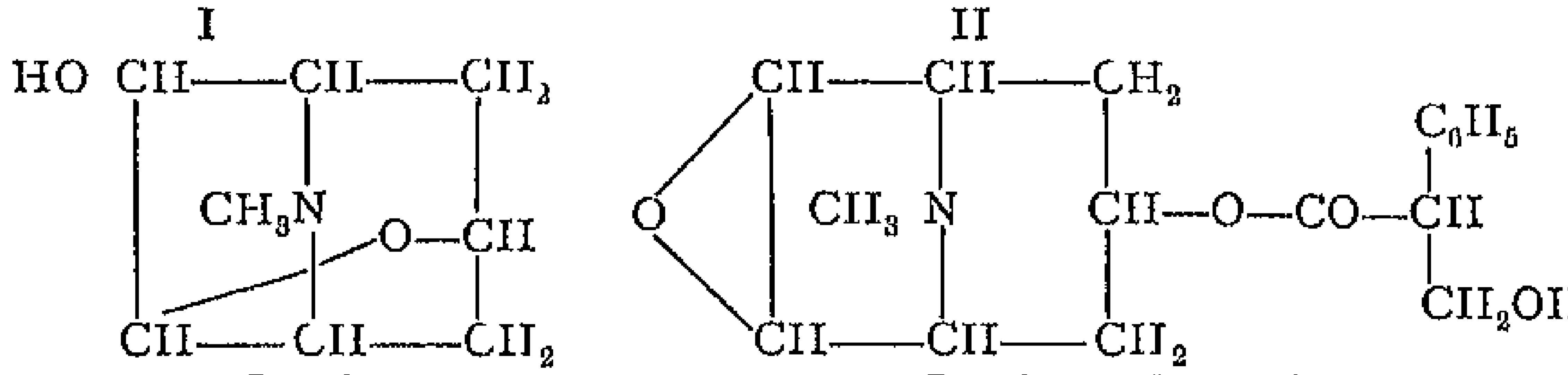
properties. With HBr in glacial acetic acid it gives an addition compound which is readily reduced to dihydro-scopoline. The latter, when heated with concentrated hydriodic acid, is reduced further to tropane.[1] This reaction establishes the constitution of the carbon framework of scopoline, and the close relationship of the compound to tropine.



Dihydro-scopoline — Tropane (scopoline)

Scopoline has also been submitted to exhaustive methylation,[2] with results which confirm the constitution (formula I) suggested for it by King.[3] Scopolamine is then represented by formula II.

I — II



Scopoline — Scopolamine (hyoscine)

The physiological action of hyoscine and scopolamine is sedative, without the deleterious secondary effects of atropine. In mydriatic action the alkaloid is many times more powerful than atropine. Scopolamine is preferable to hyoscine and is largely used as a mydriatic and sedative.

2. THE COCA ALKALOIDS

The leaves of *Erythroxylon coca* contain a large number of alkaloids. In addition to the hygrines, already described on pp. 678 *et seq.*, there are present the following:—

Cocaine	$C_{17}H_{21}NO_4$
Cinnamyl-cocaine	$C_{19}H_{23}NO_4$
α-Truxilline	$(C_{19}H_{23}NO_4)_2$
β-Truxilline	$(C_{19}H_{23}NO_4)_2$
Benzoyl-ecgonine	$C_{16}H_{19}NO_4$
Tropacocaine	$C_{15}H_{19}NO_2$

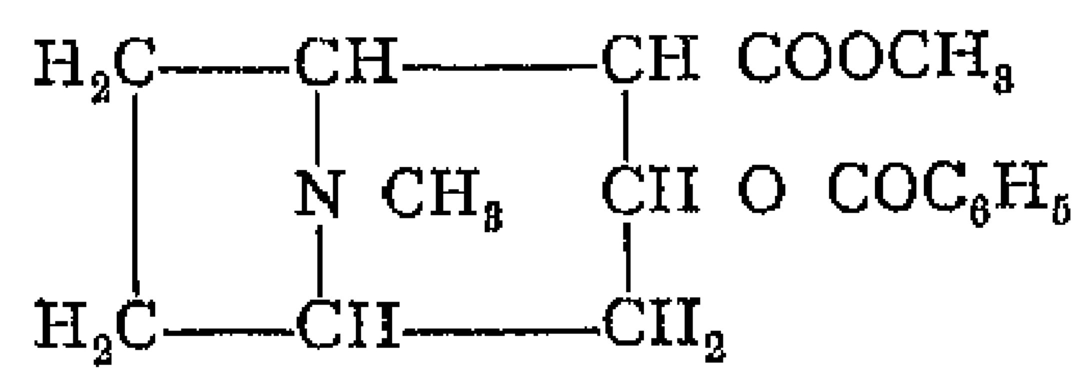
All these compounds are tropane derivatives and therefore contain a pyrrolidine nucleus. With the exception of tropacocaine they all yield ecgonine as the basic product of decomposition, and stand in close relationship to the Solanaceæ alkaloids.[1]

[1] K. Hess and co-workers, *Ber.*, 1915, 48, 2057; 1918, 51, 1007. [2] Hess, *Ber.*, 1919, 52, 1947; Gadamer and Hammer, *J. C. S.*, 1921, 120, A, i, 588. [3] King, *J. C. S.*, 1919, 115, 486.
[1] Compare the conversion of cocaine into atropine, pp. 690 and 694.

Before reading the following description of the coca alkaloids, reference should be made to the preceding pages (691 *et seq.*) dealing with ecgonine.

Among all the coca alkaloids only *l*-cocaine is of therapeutic value, the others being without particular physiological action. These inactive alkaloids, however, can be utilised for the production of *l*-ecgonine (Liebermann).

Cocaine, *methyl ester of benzoyl-ecgonine*.



Corresponding to the different stereoisomeric ecgonines (see p. 691), three stereoisomeric cocaines are known, namely *l*-cocaine, *d*-cocaine (*d*-ψ-cocaine) and *i*-cocaine; to these must be added the structurally isomeric α-cocaine derived from α-ecgonine (see p. 694).

Of these alkaloids, *l*-cocaine is the most valuable and most important. It is highly prized as a local anæsthetic and, owing to the short length of time during which its effect is operative, is largely used in eye surgery and dentistry.[1] It is employed in the form of its hydrochloride and cannot be used for producing prolonged anæsthesia, on account of its poisonous properties.

Occurrence, Disruption Products and Preparation of l-*Cocaine*

l-Cocaine was first isolated by Niemann in 1860 from Peruvian coca leaves (Erythroxylon coca). It crystallises in prisms melting at 98°, and is usually obtained from the above source by extraction with high-boiling petroleum.

On being boiled with water it is hydrolysed to methyl alcohol and benzoyl-ecgonine.

$$\underset{\text{Cocaine}}{C_{17}H_{21}NO_4} + H_2O = \underset{\text{Benzoyl ecgonine}}{C_{16}H_{19}NO_4} + CH_3OH$$

More powerful hydrolysis by means of mineral acids, baryta-water, or caustic alkali results in the benzoyl-ecgonine undergoing further decomposition into *l*-ecgonine and benzoic acid.

$$\underset{\text{Cocaine}}{C_{17}H_{21}NO_4 + 2H_2O} = \underset{\text{Ecgonine}}{C_9H_{15}NO_3} + \underset{\text{Benzoic acid}}{C_7H_6O_2} + \underset{\text{Methyl alcohol}}{CH_3OH}$$

These reactions led to the conclusion that cocaine is the methyl ester of benzoyl-ecgonine, and prepared the way for its preparation from ecgonine.

[1] For the work of A. Einhorn dealing with the relation between the constitution and physiological action of organic compounds, see *Ann.*, 1900, **311**, 26, 154.

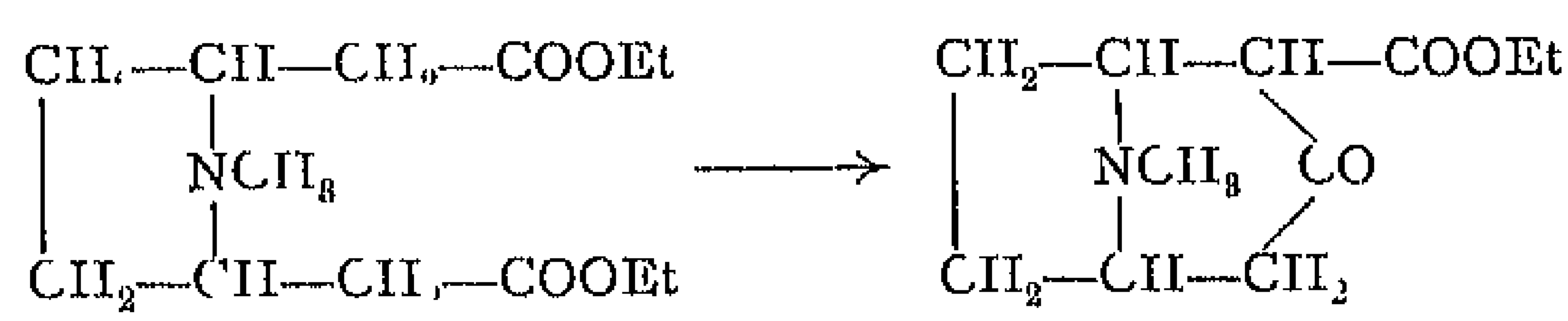
A partial synthesis of *l*-cocaine on these lines was first effected by Merck, by heating *l*-ecgonine with benzoic anhydride and methyl iodide

$$C_8H_{13}N\begin{cases}COOH\\OH\end{cases} + (C_6H_5CO)_2O + CH_3I$$
Ecgonine
$$= C_8H_{13}N\begin{cases}COOCH_3\\O\ COC_6H_5\end{cases} + HI + C_6H_5\ COOH$$
Cocaine

The conversion of ecgonine into cocaine may also be brought about by other methods of esterification According to Liebermann,[1] cocaine is obtained in good yield when *l*-ecgonine is treated in concentrated aqueous solution with benzoic anhydride, and the benzoyl-*l*-ecgonine so obtained is esterified with methyl alcohol in the presence of hydrochloric or sulphuric acid[2] Since considerable amounts of *l*-ecgonine can be prepared from the therapeutically valueless alkaloids found with natural cocaine (*cf* p 692), the above method of increasing the supply of *l*-cocaine is of special importance

Synthetic Cocaines and their Resolution

Pseudococaine, the racemic form of the *d*-pseudococaine which is present in small amount in the coca-plant, has been synthesised by Willstätter, the first stage being the intramolecular condensation of N-methyl-pyrrolidine-diacetic ester This reaction resembles an *internal* acetoacetic ester condensation, and leads to the formation of tropinone carboxylic ester



Tropinone carboxylic acid had previously been obtained by treating sodio-tropinone with carbon dioxide (see p 693) and without being isolated was reduced to *r*-ecgonine By the above condensation the ester may be prepared directly The same ester was also obtained using a modification of Robinson's method Willstätter found that when succindialdehyde is allowed to react with methylamine and the monoester of acetone dicarboxylic acid (p 689), carbon dioxide may be detached from the free carboxyl group in the resulting compound to give the ester of tropinone carboxylic acid

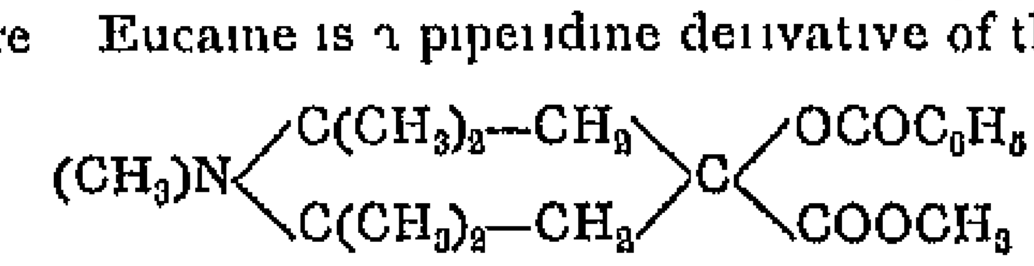
[1] *Ber*, 1888, 21, 3196, 1894, 27, 2051 [2] Other esters of benzoyl *l* ecgonine are obtained by use of the corresponding alcohols These produce the same physiological effects as *l* cocaine, over which they have no special advantage

Two Racemic Ecgonines.—Methyl tropinone carboxylate, on being reduced with sodium amalgam in weak acid solution, gave a mixture from which the methyl esters of *r*-pseudoecgonine and *r*-ecgonine were isolated. The former bears the same relationship to natural *d*-cocaine (*d*-pseudococaine) as the latter does to ordinary *l*-cocaine. Pseudotropine is also formed as a by-product in the above reduction, owing to loss of carbon dioxide from the carboxyl group.

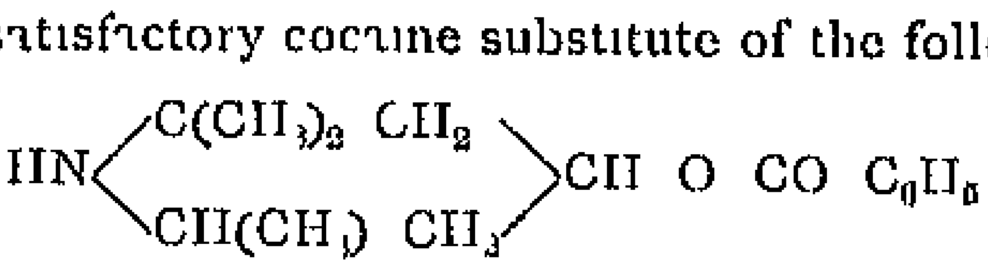
Resolution of the racemate.—The benzoyl derivative of the second racemic ester, which is the more important owing to its closer connection with ordinary cocaine, was resolved by the recrystallisation of its di-*d*-tartrate. After removing tartaric acid, the less soluble salt of the *l*-base gave an ester identical with ordinary cocaine. Among the various cocaines, two *d*-, two *l*- and the two *r*-isomerides have now been prepared in the pure state.[1]

Psicaine[2].—As already stated, two racemic alkaloids were prepared during the cocaine syntheses, one of which corresponds to natural *l*-cocaine. The other, *r*-pseudococaine (ψ-cocaine), m.p. 81.5°, was subsequently converted into the corresponding ecgonine (by removal of the benzoyl group) and the latter resolved by means of bromocamphorsulphonic acid. The *d*-pseudococaine obtained by benzoylation of the *d*-pseudoecgonine ester was found to possess the most powerful anæsthetic action, coupled with relatively low toxicity. Its tartrate, $C_{17}H_{21}O_4N,C_4H_6O_6$, is known as psicaine, and forms a microcrystalline powder, $[\alpha]_D^{20}$ + 43° (in 5 per cent. aqueous solution).

Eucaine is obtained from triacetonamine, and is a substitute for cocaine. The similar anæsthetic action of these two substances may be explained by their similarity in structure. Eucaine is a piperidine derivative of the formula



β-Eucaine is a more satisfactory cocaine substitute of the following structure:



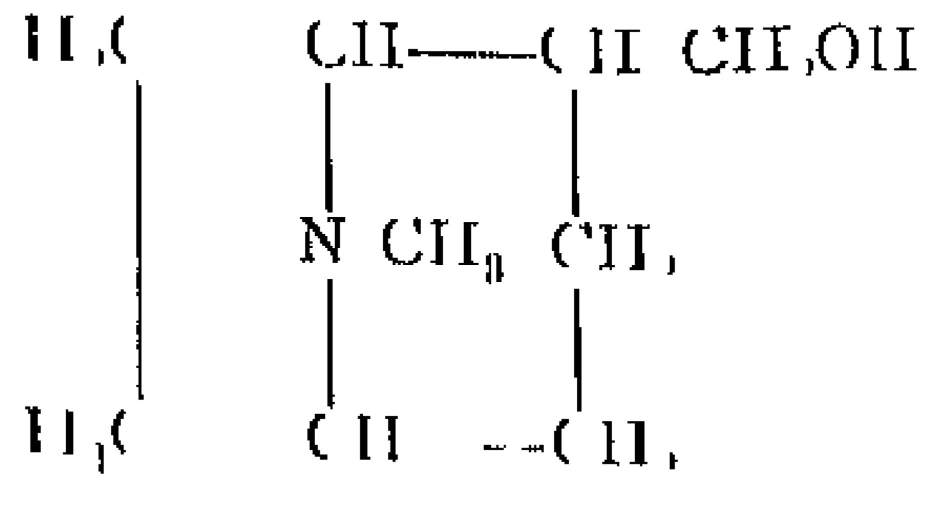
Homotropeines and Eccaine from Cocaine[3]

Starting from ecgonidine (anhydro-ecgonine), which is easily obtained from cocaine, J. v. Braun prepared in succession ecgonidine ethyl ester, hydro-ecgonidine ethyl ester, and finally, by reducing the carbethoxy group, obtained the amino alcohol I., *homotropine* (m.p. 85°).

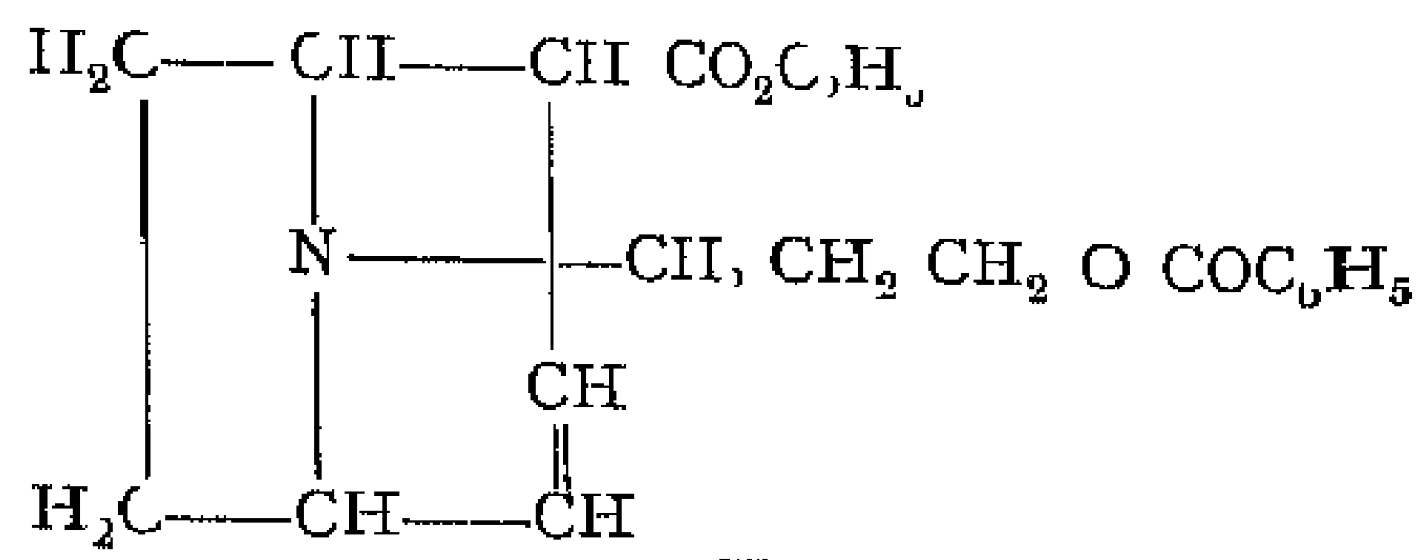
Like tropine, this compound contains a hydroxyl group in the γ-position to nitrogen, and can be esterified with various acids,

[1] R. Willstätter, Pfannenstiehl and Bommer, *Ann.*, 422, 1, 15. [2] R. Willstätter, *Münch. Med. Wochenschr.*, 1924, 71, 849; R. Willstätter and Gottlieb, *Ann.*, 1923, 434, 111. [3] J. v. Braun and Müller, *Ber.*, 1918, 51, 235.

including tropic acid Physiological investigation showed that the acidyl derivatives of homotropine—known as *homotropeines*—possess the same properties as the tropeines, and that homotropine tropate, **mydriasine**, is a mydriatic of the strength of atropine



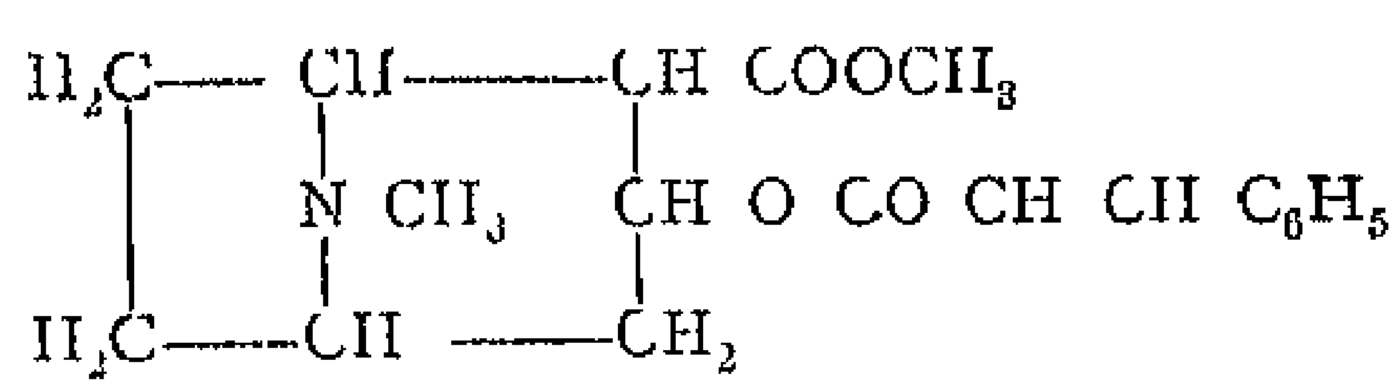
I



II

Eccaine (formula II) is obtained from cocaine in the following stages Cocaine is demethylated to cyano-norcocaine, and the latter hydrolysed to norecgonidine and esterified The secondary nitrogen atom in norecgonidine ethyl ester is then linked up with a γ-benzoyl-oxypropyl group Eccaine is not only a stronger anæsthetic than cocaine but is also non-toxic, and can readily be sterilised in aqueous solution Consequently it is an anæsthetic of ideal properties [1] It is an oil and gives a hydrochloride of melting-point 117°

Cinnamyl cocaine, *methyl ester of cinnamyl ecgonine*



l-Cinnamyl cocaine is found in practically all varieties of coca, particularly in that of Java It was investigated by Liebermann,[2] and prepared from *l*-ecgonine by the action of cinnamic anhydride and subsequent esterification of the cinnamyl derivative with methyl alcohol and hydrochloric acid It crystallises from hot benzene ligroin solution in needles of melting point 121°

Alkaloids of the Lupin Group

The following alkaloids contained in the various lupin families were originally investigated by E Schmidt[3] Their constitution is now being examined in detail

Lupinine, $C_{10}H_{19}ON$, in *Lupinus luteus* and *L niger*

Sparteine, $C_{15}H_{26}N_2$, in *L luteus* and *L niger*

Lupanine, $C_{15}H_{24}ON_2$, occurs in the racemic and laevo forms in *Lupinus albus*, *Lupinus angustifolius* and *Lupinus perennis*

The best expression for the constitution of sparteine, which is in agreement with all reactions of this compound so far known, is probably a formula in which two norhydrotropidine rings are linked together by a methylene group [4]

[1] See J v Braun and Müller, *Ber*, 1918, 51, 235 [2] *Ber*, 1888, 21, 3373 [3] E Schmidt, *J C S*, 1897, 72, A, i, 645 See also *J C S Ann Rep*, 1928, 194 [4] Wackernagel and Wolffenstein, *Ber*, 1904, 37, 3238 Scholtz, *J C S*, 1906, 90, A, i, 379 Ahrens, *Ber*, 1905, 38, 3268 Moureu and Valeur, *C r*, 1912, 154, 827

The simultaneous occurrence of sparteine and lupinine in yellow lupins points to the probability of a constitutional relationship between these two alkaloids.[1]

From an examination of the degradation products of lupinine, Willstätter and Fourneau[2] conclude that this base is a primary alcohol and contains a ring system analogous to that in the "second half" of cinchonine and quinine (see p. 708).

IV.—ALKALOIDS OF THE QUINOLINE GROUP

In this section are included the important Cinchona bases, quinine and cinchonine, together with the Strychnos bases, strychnine and brucine.

Quinine and Cinchonine

Cinchona or Peruvian bark, which has been used in Europe since the middle of the seventeenth century in the treatment of fevers, is obtained from various trees of the Cinchona family found mainly in Bolivia and Peru. It contains, in addition to a tannin and quinic acid, a series of alkaloids which are closely related to one another in structure. The most important of these are *quinine*, $C_{20}H_{24}N_2O_2$, to which the curative action of the bark is chiefly due, and *cinchonine*, $C_{19}H_{22}N_2O$.

Quinine generally crystallises with 3 mols. H_2O, and in the anhydrous condition melts at 177°; it separates from alcohol and ether in shining needles. It is present in yellow calisaya bark to the extent of 2 to 3 per cent., has an alkaline reaction, a bitter taste, and as a diacid base forms neutral and acid salts. Quinine is one of the most valuable medicines, especially in the treatment of intermittent fevers such as malaria and swamp fever, and is an antidote against many infections caused by micro-organisms.

Cinchonine accompanies quinine and is found in particularly large amounts in grey cinchona bark (*Cinchona Huanaco*), in which it occurs up to 2.5 per cent. It crystallises from alcohol in white prisms, sublimes readily and melts at 255°. As a febrifuge it is less active than quinine.

Quinine and cinchonine are similarly constituted, and therefore the results obtained by the investigation of these compounds have often supplemented one another. In many cases information gained with regard to cinchonine has been applied without modification to quinine.

Both alkaloids were discovered in the year 1820 by Pelletier and Caventou, and their constitutional formulæ have been deduced from evidence gradually accumulated from a large number of investigations.

As already stated, the composition of cinchonine is $C_{19}H_{22}N_2O$, and that of anhydrous quinine, as determined by Liebig, is $C_{20}H_{24}N_2O_2$. In their empirical formulæ, therefore, these two bases differ in that

[1] Willstätter and Marx, *Ber.*, 1904, **37**, 2351. [2] Willstätter and Fourneau, *Ber.*, 1902, **35**, 1910.

quinine contains one atom of carbon, one atom of oxygen and two atoms of hydrogen more than cinchonine

Cinchonine and quinine each possess two tertiary nitrogen atoms[1]

One oxygen atom in quinine is contained in a hydroxyl and the other in a methoxyl group

The presence of a hydroxyl group in quinine is indicated by several reactions For example, quinine forms a monobenzoyl derivative (Schutzenberger), a mono acetyl derivative (Hesse), and a silver salt of the composition $C_{20}H_{23}AgN_2O_2$ (Skraup)

The existence of a methoxyl group is shown by the formation of methyl chloride (accompanied by intramolecular rearrangement) when quinine is heated with concentrated hydrochloric acid In this case the other primary reaction product is *apoquinine*, which in turn gives a diacetyl derivative and therefore contains two hydroxyl groups

$$\underset{\text{Quinine}}{C_{19}H_{20}N_2(OH)(OCH_3)} \qquad\qquad \underset{\text{Apoquinine}}{C_{19}H_{20}N_2(OH)_2}$$

Proof that the oxygen atom of cinchonine is also present in a hydroxyl group is supplied by reactions similar to those quoted above for quinine, *e g* by the formation of acyl derivatives

Information as to the position of the hydroxyl group and the general structure of the cinchona alkaloids has been gained largely by the decompositions of these compounds carried out by Skraup, Konigs and v Miller

Decomposition of Quinine and Cinchonine by Fusion with Potash and by Oxidation

Fusion of these alkaloids with potash led to the conclusion that cinchonine contains a quinoline or lepidine group, and that quinine is derived from 6-methoxy-lepidine This is in complete agreement with the results obtained by the oxidation of the alkaloids

When oxidised with a solution of chromic acid in sulphuric acid solution, cinchonine and quinine break up, on the one hand, into the 4-carboxylic acids of quinoline and of 6-methoxy-quinoline (known respectively as cinchoninic acid and quininic acid), and on the other, into derivatives of pyridine Hence the molecule of the cinchona alkaloids must contain these two ring systems linked together

The carboxylic acids of quinoline were soon identified as such, thus establishing the presence of a quinoline nucleus ("quinoline half") in the alkaloids

On the other hand, the investigation of the pyridine derivatives (cincholoipon, meroquinene, cincholoiponic acid and loiponic acid) proved to be exceedingly difficult, and has only recently been brought to a successful issue For a long time nothing was known of the

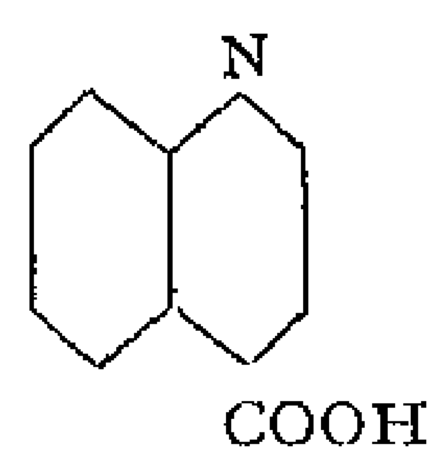
[1] Skraup and Koneck, *Ber*, 1893, 26, 1968

constitution of that part of the molecule giving rise to the pyridine compounds, and it was described briefly by Skraup[1] as the "second half" of the cinchona alkaloids. From the following it will be seen that this term is used for the grouping ($C_{10}H_{16}NO$)—, which in cinchonine is combined with the quinoline residue (C_9H_6N)—, and in quinine with 6-methoxy-quinoline residue ($CH_3O \cdot C_9H_5N$)—.

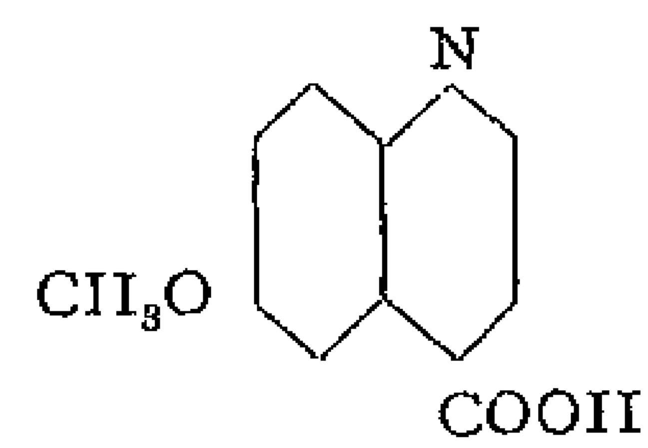
Constitution of the "Quinoline Half" of Quinine and Cinchonine

The key to the constitution of the "quinoline half" lies in the following facts:

1. When cinchonine is subjected to energetic oxidation, about 50 per cent. of the product consists of *cinchoninic acid*, which is identical with *quinoline-4-carboxylic acid*.



Cinchoninic acid,
Quinoline-4-carboxylic acid.

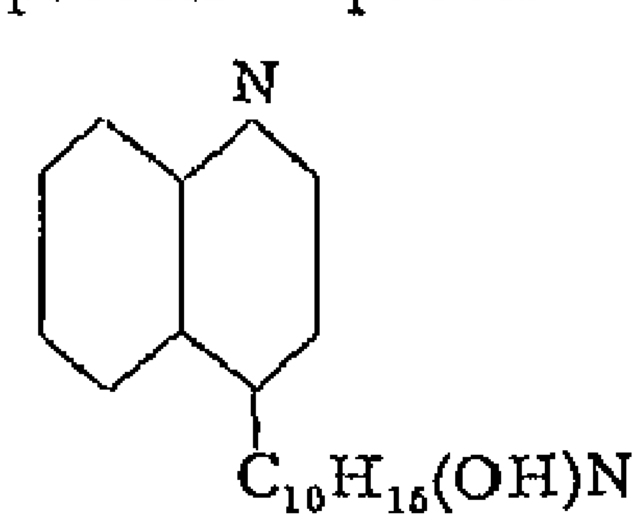


Quininic acid,
6-Methoxy cinchoninic acid.

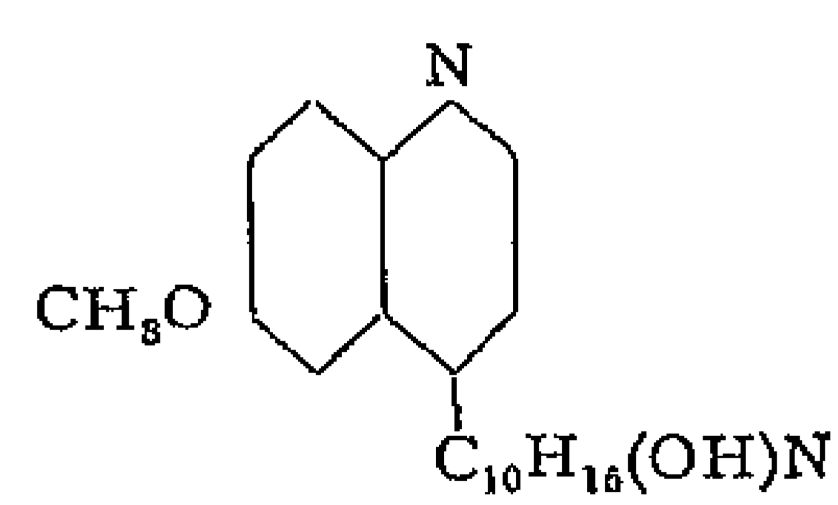
From this it follows that cinchonine is a derivative of quinoline, containing a side chain in the 4-position. The hydroxyl group of cinchonine is also present in the side chain because, had it been situated in the quinoline nucleus, the oxidation product would have been a hydroxy-cinchoninic acid.

The composition of this side chain must be $C_{10}H_{15}(OH)N$, *i.e.*, the difference between the formula for cinchonine, $C_{19}H_{21}(OH)N_2$, and that of the quinoline radical, C_9H_6N. Hence the structure of cinchonine may be represented provisionally by formula I.

I



II



2. When quinine is energetically oxidised with chromic acid[2] it gives an acid $C_{11}H_9NO_3$, known as quininic acid. The difference between this compound and cinchoninic acid, $C_{10}H_7NO_2$, is the same as that between quinine and cinchonine.

Quininic acid was shown by Skraup to be 6-methoxy cinchoninic

[1] Skraup, *Monats.*, 1888, 9, 783.

[2] Skraup, *Monats.*, 1881, 2, 591; 1883, 4, 695. *Ber.*, 1879, 12, 1106; 1883, 16, 2684.

acid (see p 657) From this it was concluded that quinine is a methoxy-cinchonine, and that the methoxyl group replaces the hydrogen atom corresponding to position 6 of the quinoline nucleus present in cinchonine Quinine was therefore represented by formula II

In the above oxidations, the disruption of the "second half" of cinchonine and quinine yields in each case the same derivatives of pyridine The "second half" of cinchonine must therefore be the same as the "second half" of quinine, and the difference in the two alkaloids may be summarised in the statement that the former is a derivative of quinoline and the latter of 6-methoxy-quinoline [1]

Information as to the structure of the cinchona bases has also been obtained by the investigation of certain intermediate products of oxidation, known as "tenines"

Skraup found that the formation of *cinchotenine* by the oxidation of cinchonine with potassium permanganate is accompanied by the production of formic acid, according to the equation

$$\underset{\text{Cinchonine}}{C_{19}H_{22}N_2O} + 4O = \underset{\text{Cinchotenine}}{C_{18}H_{20}N_2O_3} + \underset{\text{Formic acid}}{H \cdot COOH}$$

Similarly quinine, when oxidised with potassium permanganate, gives formic acid and the corresponding compound, *quitenine*

$$C_{20}H_{24}N_2O_2 + 4O = C_{19}H_{22}N_2O_4 + H \cdot COOH$$

The relationship between cinchonine and cinchotenine is established as follows When cinchotenine is oxidised with chromic acid it gives cinchoninic acid The tenine must therefore have been formed from cinchonine by alterations in the *second half* of the molecule Further, the hydroxyl group of cinchonine is still present as such in cinchotenine, although the acid properties of the latter are due to the additional presence of a carboxyl group

Since in any case cinchonine only possesses one oxygen atom, and this is contained in a hydroxyl group which is found unchanged in cinchotenine, it follows that the carboxyl must have originated in the oxidation of a group consisting solely of carbon and hydrogen

Some information about this group is given by the following facts [2]

Whereas cinchonine has the power of combining directly with hydrogen halide, cinchotenine has not The formation of the carboxyl group has therefore been accompanied by the disappearance of a group

[1] Demethylated quinine—*i e*, the derivative of 6 hydroxy-quinoline corresponding to quinine—is found in a bark obtained from *Remija pedunculata* It is known as **cupreine**, and on methylation is converted into quinine Thus quinine is the methyl ether of cupreine, to which it is related as anisole to phenol, and, as will be seen later, as codeine is to morphine The higher homologues of hydrocupreine have a strong disinfectant action towards pathogenic bacteria **Eucupine**, the hydrochloride of iso *amyl hydrocupreine*, and **vuzine**, or iso *octyl hydrocupreine*, are commercial products Eucupine also possesses an anaesthetic action Klapp, *C*, 1919, I, 122 Morgenroth, *Ber Deut pharm Ges*, 1919, 29, 233 [2] Skraup, *Monats*, 1897, 18, 162

with unsaturated properties. During the destruction of this group only one carboxyl group is formed, and a carbon atom is detached as formic acid. Further, cinchotenine is easily transformed into cincholoiponic acid, which must be regarded as a closed ring compound. Hence the unsaturated group must be present as a side chain. All these facts can only be satisfactorily explained by assuming that cinchonine contains a *vinyl group*. This group unites with hydrogen halides, and on oxidation is ruptured at the double bond with the production of a carboxyl group and formic acid.

$$R \cdot CH : CH_2 + 4O = R \cdot COOH + H \cdot COOH$$

$$\underset{\text{Cinchonine}}{(C_{17}H_{18}N_2)\left<\begin{matrix} CH : CH_2 \\ OH \end{matrix}\right.} \longrightarrow \underset{\text{Cinchotenine}}{(C_{17}H_{18}N_2)\left<\begin{matrix} COOH \\ OH \end{matrix}\right.}$$

The conclusions just arrived at for cinchonine can also be applied directly to quinine, which in an analogous manner may be converted into quitenine.

The property possessed by quinine and cinchonine of uniting with two atoms of bromine, or a molecule of halogen halide, is in complete agreement with the above constitution.

Constitution of the "Second Half" of Quinine and Cinchonine

Valuable information concerning the constitution of the "second half" of the cinchona bases has been obtained by Königs,[1] who examined the hydrolysis products of cinchene and quinene.

Cinchene, $C_{19}H_{20}N_2$, is the anhydro-compound of cinchonine, $C_{19}H_{22}N_2O$, and *quinene*, $C_{19}H_{19}(OCH_3)N_2$, the anhydro-compound of quinine, $C_{19}H_{21}(OCH_3)N_2O$.

In many respects, these compounds are much more reactive than the parent alkaloids, from which they are obtained by successive treatment with phosphorus pentachloride and alcoholic potash.

Hydrolytic Decomposition of Cinchene and Quinene[2]

According to experimental conditions, cinchene and quinene may take up the elements of water and decompose in two distinct ways.

1. When the anhydro-bases are boiled for a long time with concentrated hydrobromic acid, they take up *one* molecule of water and

$$\underset{\text{Cinchene}}{C_{19}H_{20}N_2} + H_2O = \underset{\text{Apocinchene}}{C_{19}H_{19}NO} + NH_3$$

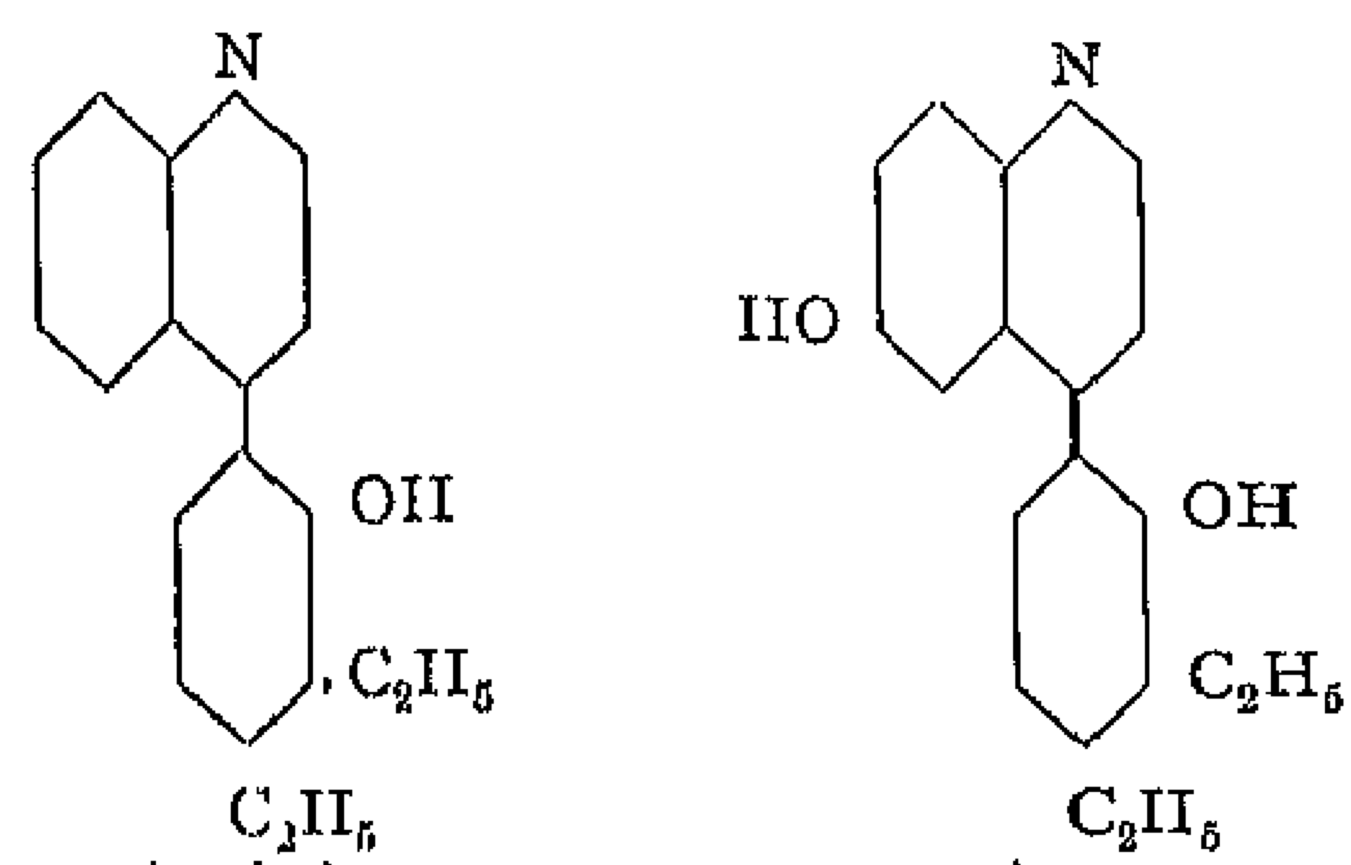
$$\underset{\text{Quinene}}{C_{19}H_{19}(OCH_3)N_2} + H_2O + HBr = \underset{\text{Apoquinene}}{C_{19}H_{19}NO_2} + NH_3 + CH_3Br$$

[1] Königs and Comstock, *Ber.*, 1884, 17, 1984; 18, 1219. [2] See *Ber.*, 1892, 25, 1511; 1894, 27, 900.

at the same time lose a molecule of ammonia. In this manner they yield derivatives of 4-phenyl quinoline, which were described by Königs and Comstock as *apocinchene* and *apoquinene* respectively.

The information gained from the investigation of apocinchene can be directly applied to the constitution of apoquinene, since the latter is easily converted into the former. Thus when apoquinene is heated at 250° with a mixture of ammonium chloride and the double compound of ammonia with zinc chloride, only the hydroxyl group present in the quinoline residue is replaced by an amino group. The amino-apoquinene so obtained can then be converted through the diazo-compound into apocinchene.

Königs showed that apocinchene and apoquinene were derivatives of 4 *o*-hydroxyphenyl-quinoline. They have the following constitutions:



Apocinchene — Apoquinene

The conversion of apoquinene into apocinchene outlined above leads to the conclusion that apoquinene is hydroxy-apocinchene, and when taken in conjunction with the facts given on p. 706, proves that the additional hydroxyl group must occupy position 6 in the quinoline nucleus. The complete analogy in the behaviour of quinene and cinchene points to the analogous structure of the two anhydro-bases. Hence it may be assumed that quinene is derived from cinchene by replacement of the hydrogen atom in position 6 in the quinoline nucleus by a methoxyl group.

2. When cinchene is heated with 20 per cent aqueous phosphoric acid at 170° to 180°, it yields *lepidine* and a compound of the composition $C_9H_{15}NO_2$, described by Königs as *meroquinene*. The hydrolysis of cinchene under these conditions therefore takes place according to the equation

$$\underset{\text{Cinchene}}{C_{19}H_{20}N_2} + 2H_2O = C_{10}H_9N + \underset{\text{Meroquinene}}{C_9H_{15}NO_2}$$

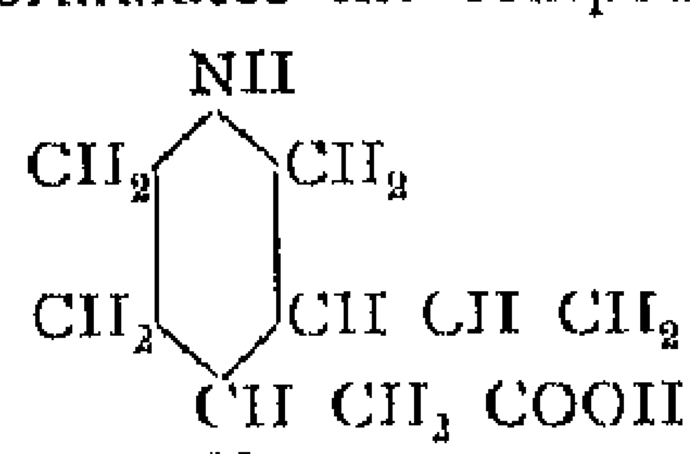
In a similar manner quinene is hydrolysed to 6-methoxy-lepidine and meroquinene.

Constitution of Meroquinene, Cincholoiponic Acid and Loiponic Acid[1]

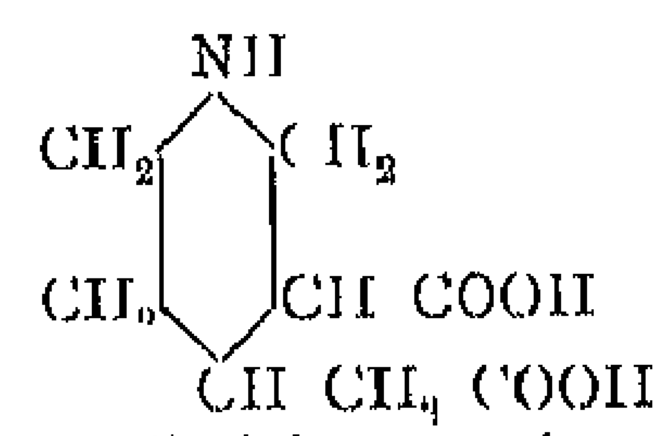
Königs found that meroquinene could be obtained by the direct oxidation of cinchonine with chromic acid, as well as by the hydrolysis of cinchene and quinene. On further treatment with an ice-cold aqueous solution of potassium permanganate and sulphuric acid, meroquinene yields *cincholoiponic acid*. This compound was also obtained by Skraup by the direct oxidation of cinchonine and quinine:

$$\underset{\text{Meroquinene}}{C_9H_{15}NO_2} + 4O = \underset{\text{Cincholoiponic acid}}{C_8H_{13}NO_4} + \underset{\text{Formic acid}}{H \cdot COOH}$$

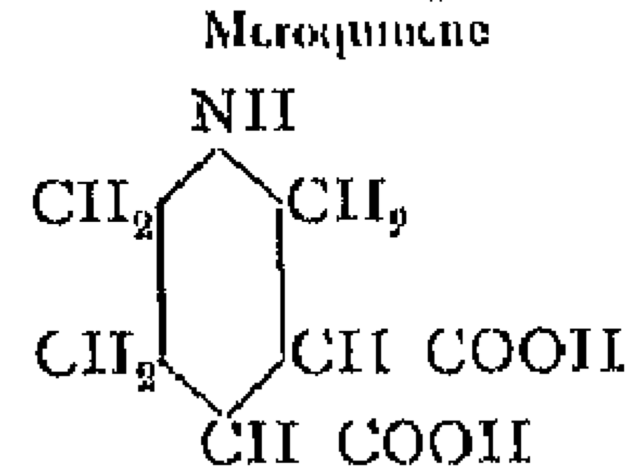
From cincholoiponic acid, by careful oxidation with potassium permanganate, Skraup isolated very small quantities of *loiponic acid*. Hence meroquinene, cincholoiponic acid and loiponic acid represent successive stages in the oxidation of the "second half" of cinchonine. Königs formulates the compounds as follows:—



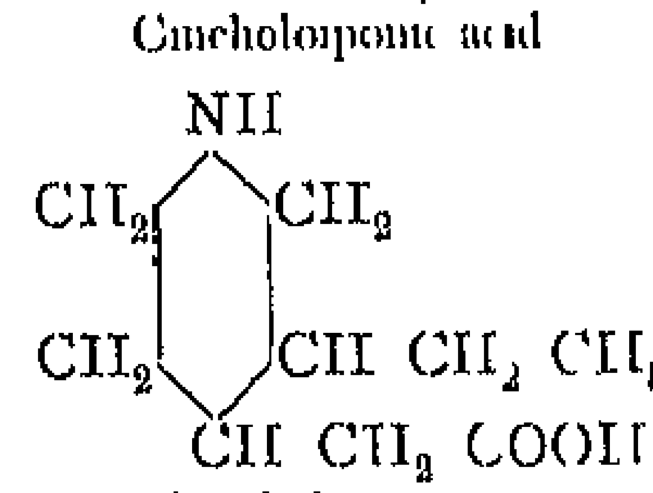
Meroquinene



Cincholoiponic acid



Loiponic acid



Cincholoipon

On reduction with zinc dust and hydriodic acid, meroquinene is converted into *cincholoipon*, the formula for which is also given above. The presence of the carboxyl groups in these products has been proved by the preparation of esters, and that of the imino group by the preparation and properties of nitrosamines, and of acetyl and N-alkyl derivatives.[2] The positions of the carboxyl groups in meroquinene and cincholoipon were finally established as a result of the synthesis of *ethyl quinuclidine*, which is described on p. 712.

The assumption that these compounds contained a pyridine nucleus was based primarily on the formation of 4-*methyl*-2-*ethyl*-*pyridine* when meroquinene is heated with a solution of mercuric chloride in hydrochloric acid, and also on the conversion of cincholoiponic acid into 4-methyl-pyridine by means of concentrated sulphuric acid.[3]

[1] Königs, *Ber.*, 1894, **27**, 904, 1501; 1895, **28**, 1986, 3150; 1897, **30**, 1326, 1332; *Ann.*, 1906, **347**, 143. Skraup, *Ber.*, 1895, **28**, 15; *Monats.*, 1896, **17**, 365. [2] P. Rabe and R. Ritter, *Ann.*, 1906, **350**, 180. [3] Skraup, *Monats.*, 1896, **17**, 368.

The most convincing proof of the presence of a pyridine nucleus in loiponic acid is due to Königs. When this compound is heated with potassium hydroxide it is transformed into an isomeric acid, which is identical with synthetic *hexahydro-cinchomeronic acid* (piperidine-3 4-dicarboxylic acid). Loiponic acid is therefore a labile form of hexahydro-cinchomeronic acid, which passes into the stable form on being heated with alkali.

The formula for cincholoiponic acid was eventually confirmed by Wohl,[1] who succeeded in synthesising both of the theoretically possible racemic compounds from β-chloro-propionacetal. These racemic compounds were resolved into the four optically active forms, one of which proved to be identical in all respects with the cincholoiponic acid obtained from quinine by Skraup.

The additional knowledge of the constitution of cinchonine and quinine gained by the study of meroquinene, cincholoipon, cincholoiponic acid and loiponic acid, may therefore be summarised as follows:—

Of the ten carbon atoms present in the "second half" of the cinchona bases, five are contained in a piperidine nucleus, two in a vinyl group, and one in a methyl group. The points at which the vinyl and methyl groups are attached to the piperidine nucleus have been determined.

The hydrolysis of cinchene and quinene to give meroquinene on the one hand, and lepidine or methoxy-lepidine on the other, indicates that the piperidine and quinoline nuclei are united by another carbon atom of the "second half," which appears as the methyl group in lepidine.

Hence the only point which still remains obscure in the constitution of the cinchona alkaloids is the mode of union of this carbon atom. In this connection Miller and Rohde have put forward a suggestion based on the hydrolytic decomposition of cinchonine and quinine, for which the original paper[2] must be consulted.

By means of moderate oxidation with chromic acid in acetic or sulphuric acid solution, Rabe[3] converted cinchonine and its isomeride cinchonidine into a ketone, which by analogy with tropinone was named *cinchoninone*. The corresponding compound, *quininone*, was obtained in a similar manner from quinine and its isomeride quinidine. The two tertiary nitrogen atoms and the vinyl group of the parent alkaloids are still present in these ketones, but the alcoholic hydroxyl group has disappeared, being changed into a ketonic group. Consequently, *cinchonine and quinine are secondary alcohols*.

On reduction, cinchoninone and quininone are converted back into cinchonine and quinine, thus definitely establishing their relationship to the original alkaloids. In addition, it will be seen that information

[1] *Ber.*, 1907, 40, 4679, 4711; 1909, 42, 627.

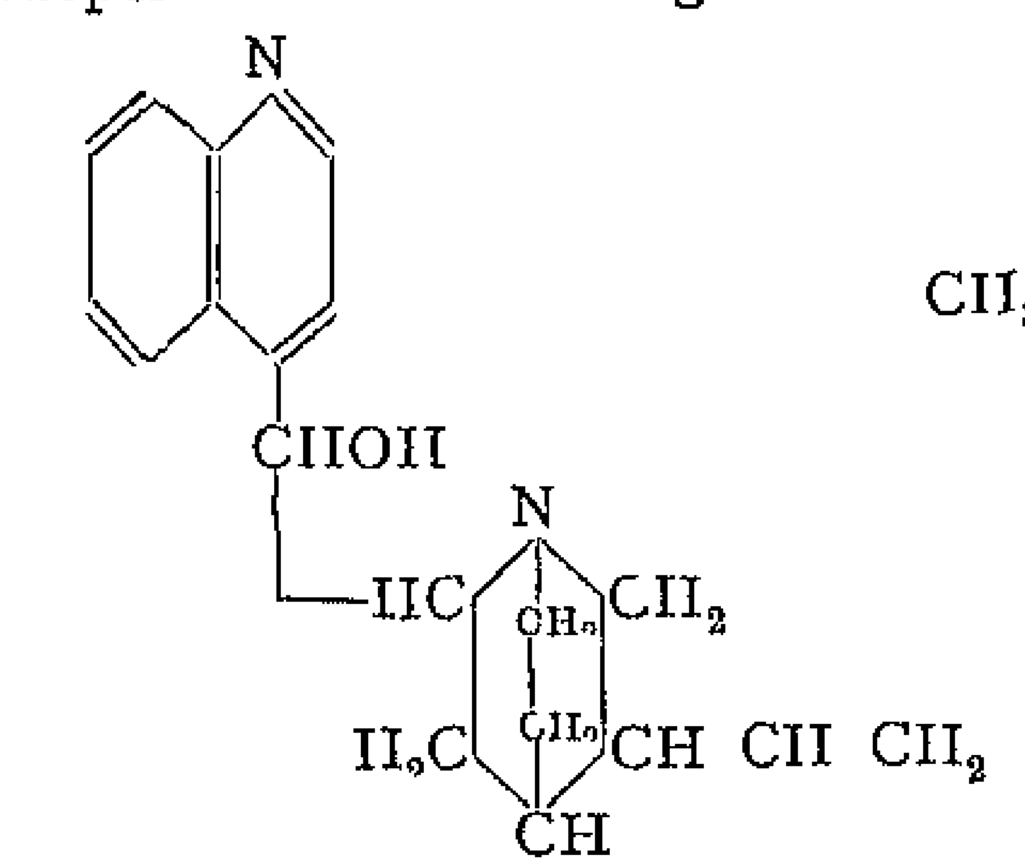
[2] Miller and Rohde, *Ber.*, 1894, 27, 1279, 1187; 1895, 28, 1056; 1900, 33, 3214.

[3] P. Rabe, *Ber.*, 1907, 40, 3281, 3655; *Ann.*, 1909, 364, 330.

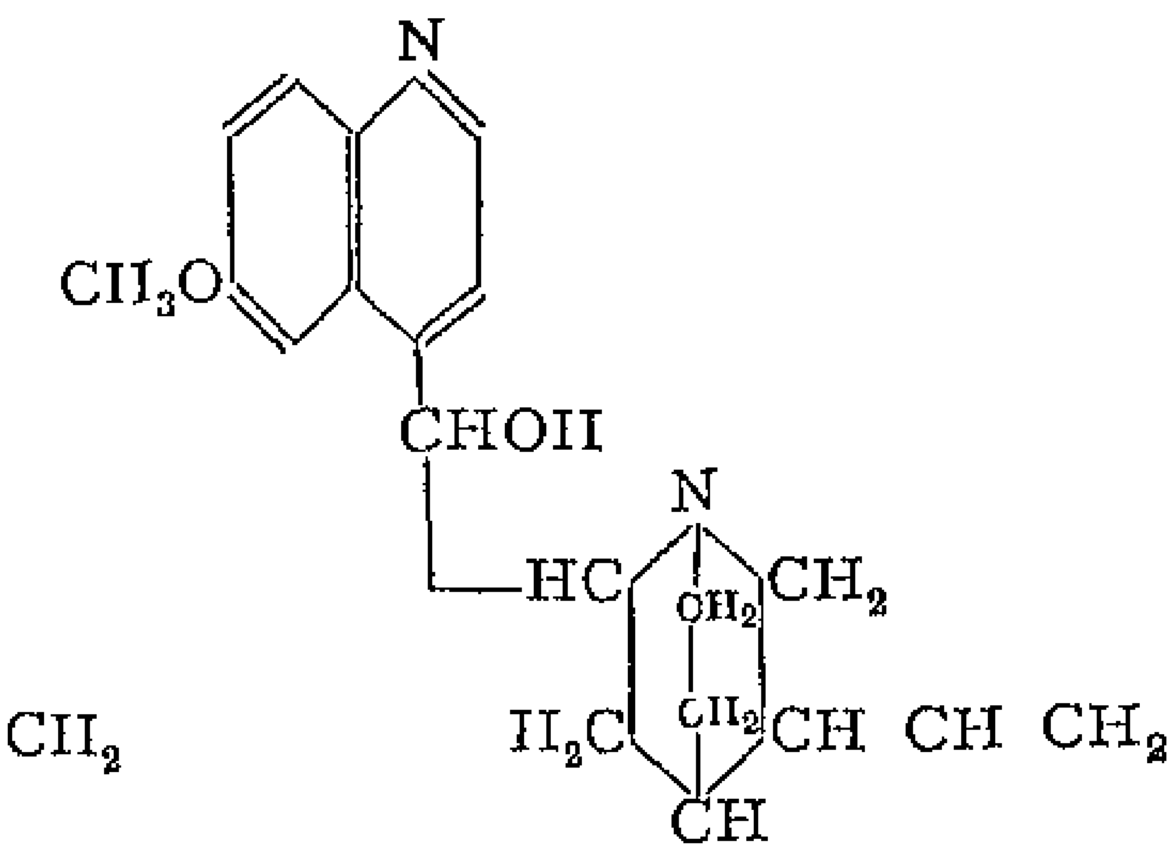
obtained from the chemical decomposition of the ketones[1] may be applied without modification to the cinchona alkaloids themselves

Constitution of Quinine and Cinchonine

The investigations described in the foregoing pages led to the adoption of the following formulæ for quinine and cinchonine —

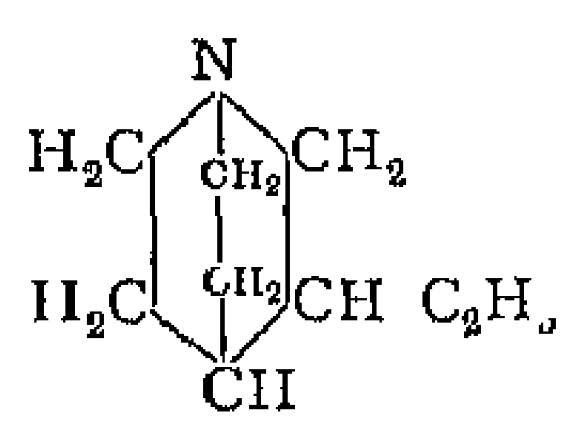


Cinchonine



Quinine

Since each of the above formulæ contains three asymmetric carbon atoms, each structure represents a possibility of eight optically active and four racemic stereoisomerides[2] Among these are **cinchonidine**, which is stereoisomeric with cinchonine, and **conchinine**, a stereoisomeride of quinine.



β Ethyl quinuclidine

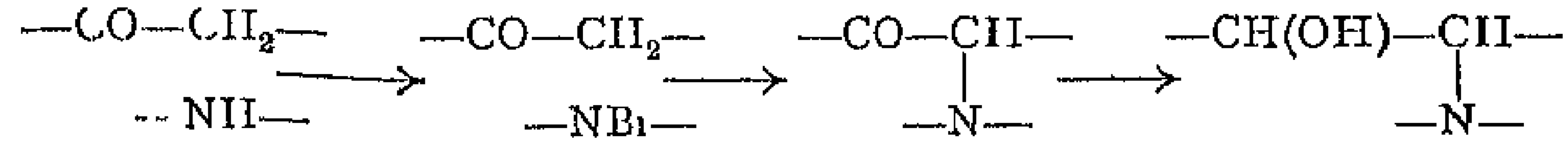
The possibility of the existence of a carbon bridge between the nitrogen atom and the 4-carbon atom of the piperidine nucleus, as shown above, has been established by the synthesis of **β-ethyl quinuclidine**[3] of the annexed structure The parent compound quinuclidine has also been synthesised[4]

Attempts to Synthesise the Cinchona Alkaloids

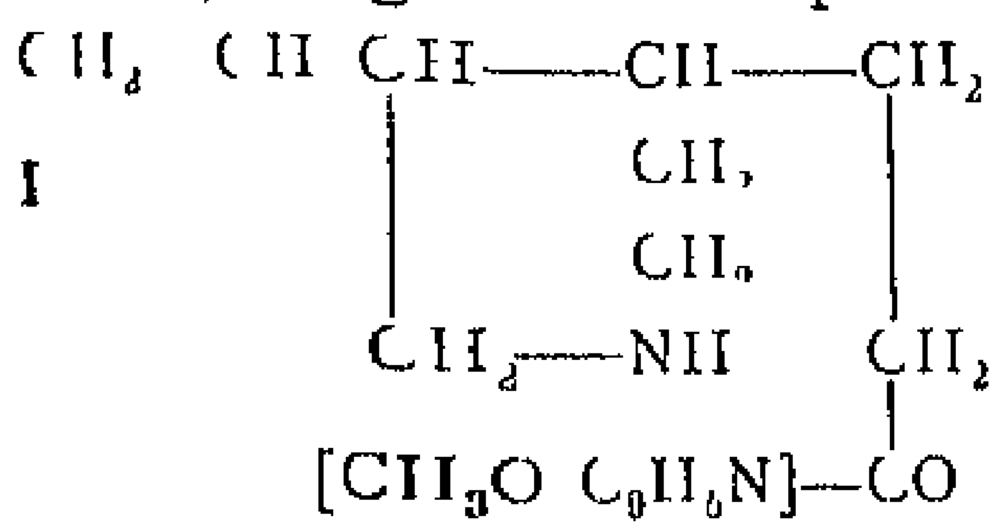
When cinchonine and quinine are heated for a long time with acetic acid, they undergo intramolecular change and yield *cinchotoxine* and *quinotoxine* respectively These *toxines* are formed from the alkaloids by conversion of the —CHOH group into —CO, accompanied by the rupture of the quinuclidine nucleus They are ketones as well as secondary bases The reverse change from the toxines into the alkaloids has not been accomplished directly as yet, but has been effected indirectly through the following stages The hydrogen atom of the imino group can be replaced by bromine to give bromo-imines,

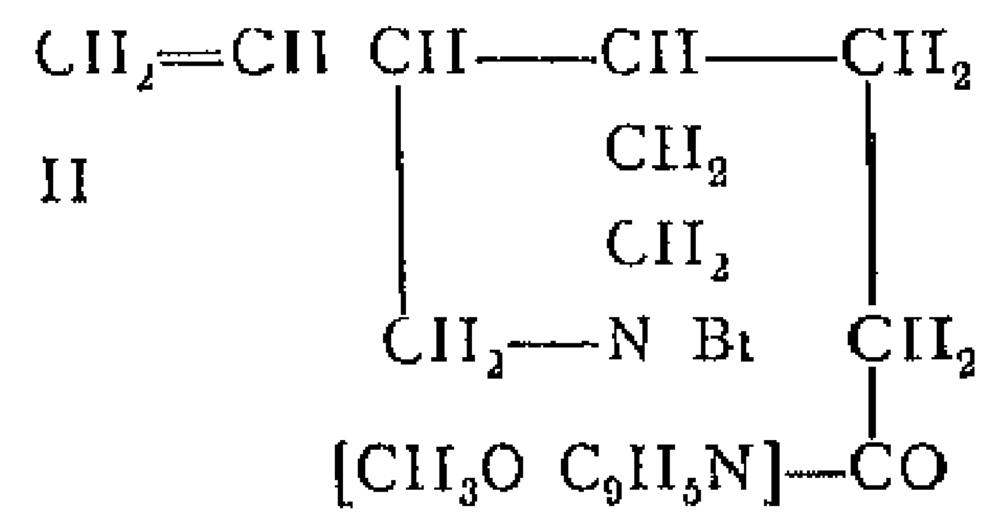
[1] P Rabe, *Ann*, 1909, 365, 353 [2] For further details and for proposals concerning the rational nomenclature of the cinchona alkaloids and related compounds, see P Rabe, *Ber*, 1922, 55, 522 [3] Konigs, *Ber*, 1904, 37, 3244 Konigs and Bernhardt, *Ber*, 1905, 38, 3049 [4] Loffler and Stietzel, *Ber*, 1909, 42, 124

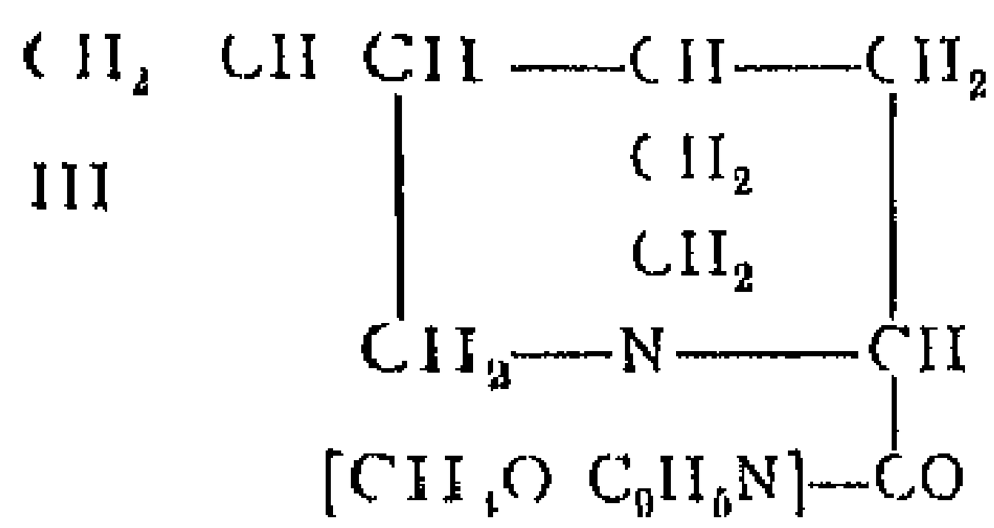
which by loss of a molecule of hydrogen bromide can be converted into the compounds quininone and cinchoninone[1] (see p 711) These reactions lead to the regeneration of the quinuclidine nucleus peculiar to the cinchona alkaloids Finally, the ketones can be reduced to the alkaloids themselves

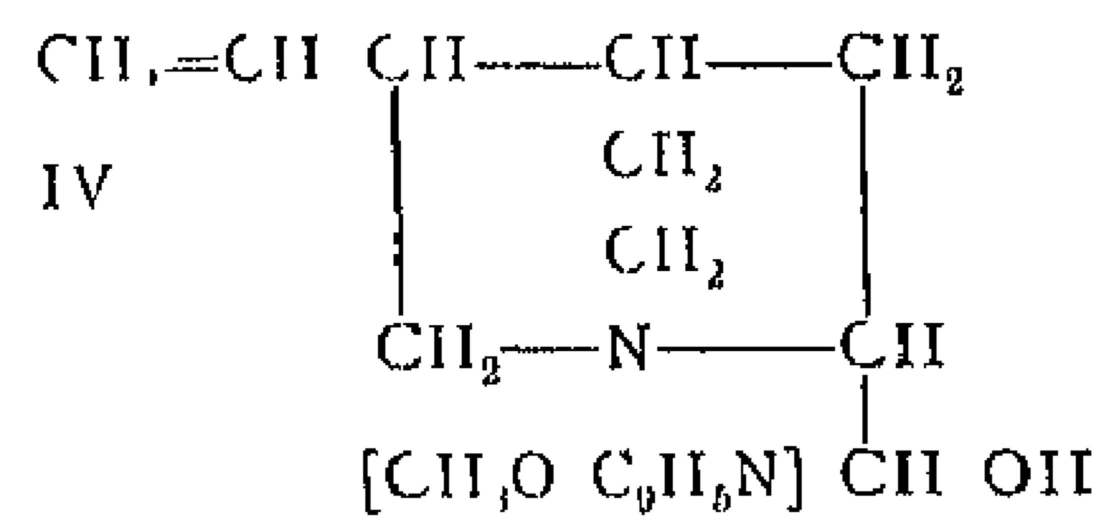


The partial synthesis of quinine from quinotoxine or quinicine[2] by this method proceeds as follows —Quinicine (I) is converted into N-bromoquinicine (II) by the action of sodium hypobromite Quininone (III) is obtained from the bromo-imine by treatment with alkali, and is then reduced to quinine (IV) by reduction in alcoholic solution, using aluminium powder in the presence of sodium ethylate



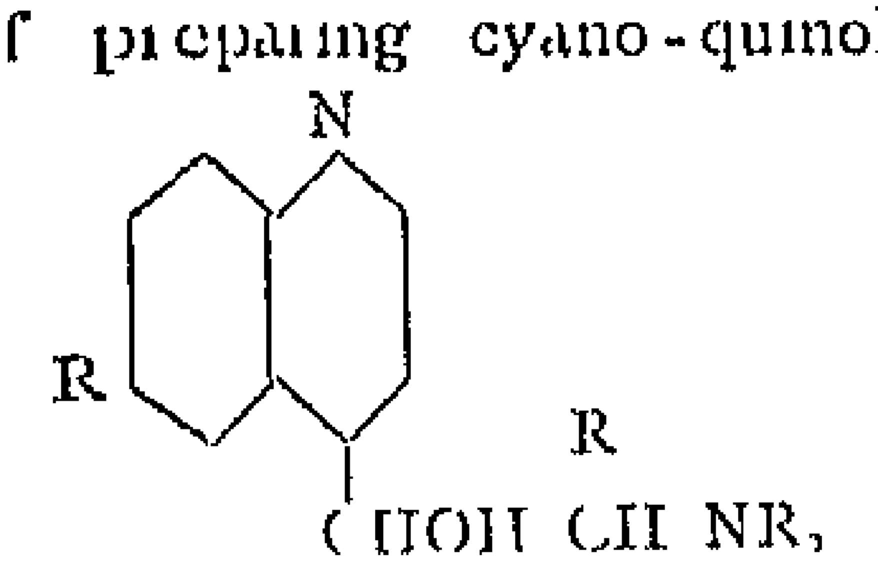






The above investigations established the position of the carbonyl group in the toxines, and revealed methods of opening up the quinuclidine nucleus of the alkaloids, as well as of converting the toxines so obtained back into the parent compounds This measure of success paved the way for a number of attempts to synthesise cinchonine and quinine, and bases closely related to them In every case the starting material was either cinchonic acid, quininic acid, or an ester or nitrile of these acids By making use of a convenient method of preparing cyano-quinolines, Kaufmann[3] succeeded in

V



R' = H or alkyloxy group

R = alkyl group

[1] P Rabe, *Ber*, 1911, 44, 2088, 1913, 46, 1023, 1026 [2] P Rabe and Kindler, *Ber*, 1918, 51, 466 [3] *Ber*, 1912, 45, 3090, 1913, 46, 57, 1916, 49, 2302 Synthesis of quininic acid, *Ber*, 1909, 42, 3776, 1911, 44, 2061, 1912, 45, 1805, 1918, 51, 116, 1922, 55, 614 Also J Halberkann, *Ber*, 1921, 54, 3079, 3090

synthesising various acids and 4-quinolyl ketones, and later obtained bases of the type V, which were closely related to the cinchona bases

The synthesis of cinchona alkaloids from derivatives of piperidine and quinoline has recently been completed by Rabe,[1] using cyano-quinolines and cinchoninic ester as his starting material From 4-methyl-pyridine (obtained from coal tar) Rabe synthesised cincho- and quinotoxines,[2] which, however, contained no vinyl group

In conclusion, it may be mentioned that hydro derivatives, such as dihydro quinine (quinotine) and dihydro-cinchonine (cinchotine), which contain an ethyl group in place of the vinyl group of cinchonine and quinine, also occur in cinchona bark They may be prepared from the last-named alkaloids by hydrogenation[3]

Plasmochine is a synthetic alkaloid having the constitution of a complex alkylamino-6-methoxy-quinoline It acts directly on the schizomes of tropical malaria and is ten times as potent as quinine

The Strychnos Alkaloids

There are three alkaloids in this series, namely strychnine, brucine and curarine Whilst numerous investigations have been carried out on the first two of these compounds, **curarine**, on the other hand, has been very little examined from the chemical standpoint In small doses it produces complete paralysis of the voluntary muscles

Strychnine occurs in Ignatius beans (the seeds of *Strychnos Ignatii*), in the seeds of the fruit of *Strychnos nux vomica*, and in other sources

It crystallises in rhombic prisms, which melt at 265° It is very insoluble in water, has a bitter metallic taste, and is one of the most powerful poisons known Regnault showed that the empirical formula of strychnine is $C_{21}H_{22}N_2O_2$ Although it contains two nitrogen atoms, it only forms stable salts with one equivalent of an acid The decomposition of strychnine has been brought about by various methods, such as distillation with zinc dust, alkalis or alkaline earths, but the results obtained so far have given no certain information as to the carbon framework of the molecule, or the function of the oxygen and nitrogen atoms. The primary decomposition products of strychnine, however, indicate that one nitrogen atom is contained in a reduced quinoline or indole ring, and that its basic character is neutralised by union with a carbonyl group.

Tafel,[4] who was the first to investigate strychnine, studied the action of methyl iodide and reducing agents on the alkaloid and its derivatives. He also examined the behaviour of strychnine towards nitric acid More recently, investigations of strychnine and brucine have been carried out by Leuchs[5] and by Perkin and Robinson The last named authors have proposed formulæ[6] for which the original literature should be consulted

Brucine, $C_{23}H_{26}N_2O_4$, is generally found with strychnine in the wood and seeds of the various strychnos plants

From hot water it crystallises in union with $4H_2O$, and from alcohol with

[1] P Rabe and co workers, *Ber*, 1913, 46, 1024, 1026, 1917, 50, 144, 1918, 51, 1360
[2] P Rabe, K Kindler and O Wagner, *Ber*, 1922, 55, 532, and see also L Ruzicka, *Helv Chim Acta*, 1921, 4, 486 [3] P Rabe, *Ber*, 1911, 44, 2088 A Skita, *Ber*, 1912, 45, 3588
[4] Tafel, *Ann*, 1891, 264, 33, 1892, 268, 229, 1898, 301, 285 [5] *Ber*, 1909, 42, 774, 2494, 1912, 45, 201, 218, 2653, 1914, 47, 536, 1552, 1919, 52, 1443, 1583, 2195, 2204, 1921, 54, 2177, 1922, 55, 564, 724, 1244, 1929, 62, 2176 [6] *J C S*, 1928, 3082, 1929, 967

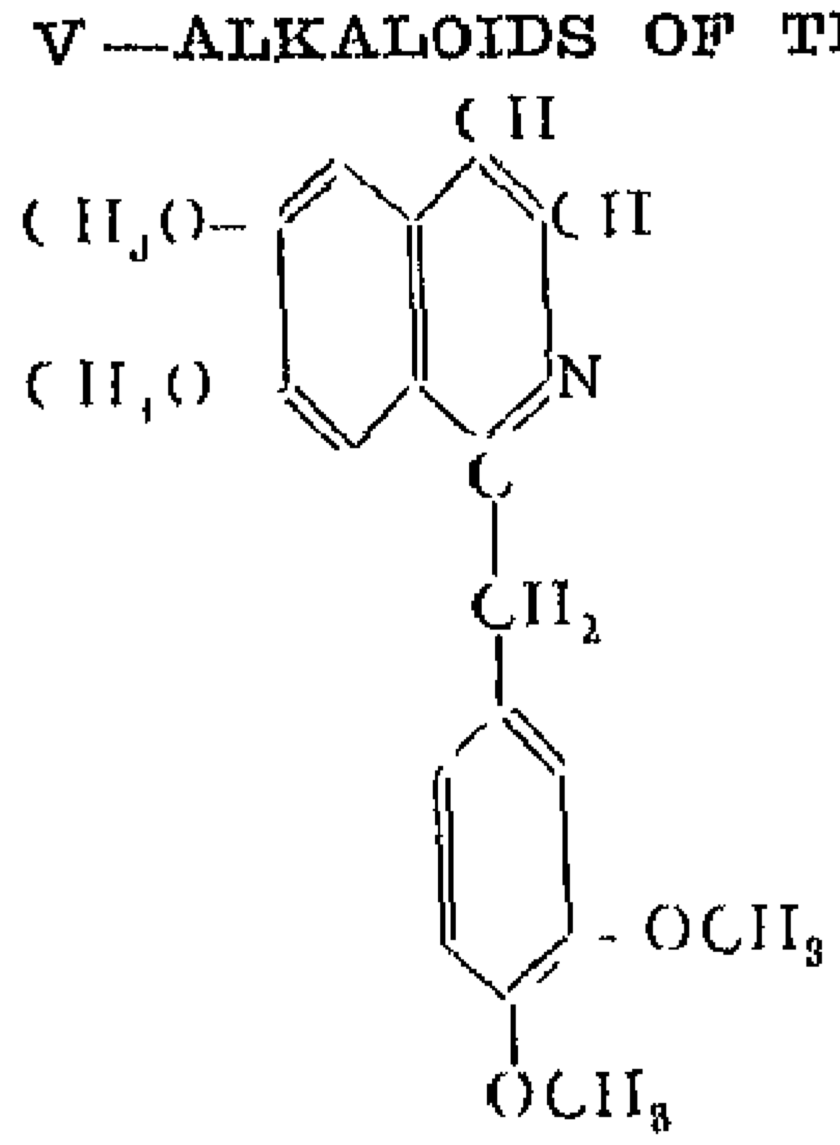
$2C_2H_5OH$. The hydrated compound melts above 100° in its own water of crystallisation. When anhydrous it melts at 178.

Brucine has the same physiological properties as strychnine, but is much less active. It also resembles strychnine in having two nitrogen atoms in its molecule and in being a monacid base. This similarity, taken with the fact that the two alkaloids occur together in nature, probably indicates a corresponding similarity in chemical constitution.

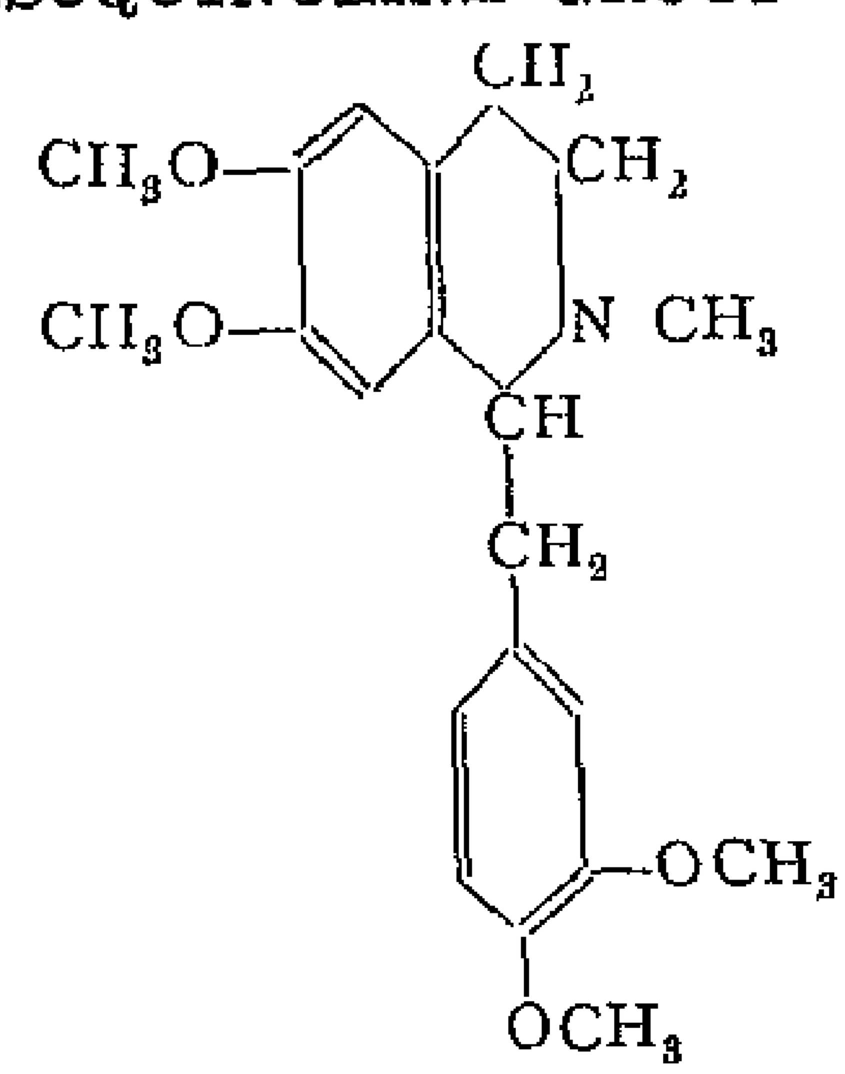
It has been shown that brucine contains two methoxyl groups, which can be estimated by Zeisel's method. In addition, Shenstone found that by the action of hydrochloric acid, methyl chloride is obtained from brucine but not from strychnine.

The formula for strychnine,[1] which is now established as $C_{21}H_{22}N_2O_2$, differs from that of brucine by the quantity $C_2H_4O_2$. Such a relationship would suggest that brucine is dimethoxy strychnine. This has yet to be proved, however, and is chiefly supported by the frequent occurrence of the two alkaloids in one and the same plant, and by their similar physiological action.

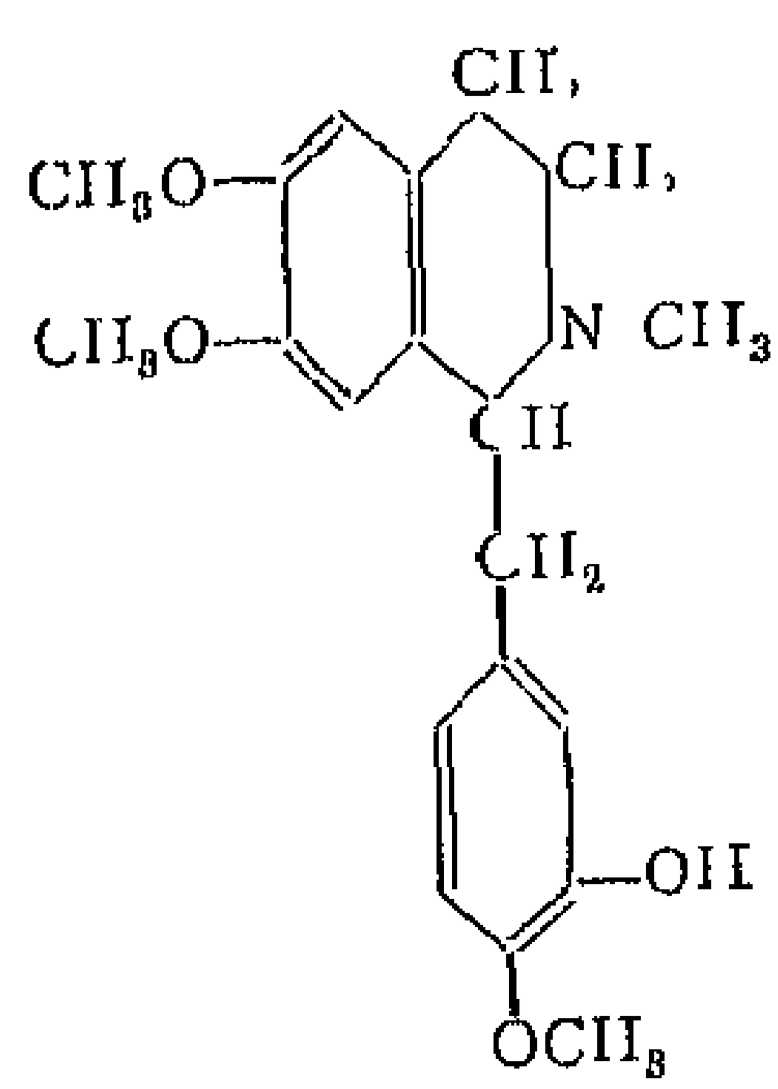
V.—ALKALOIDS OF THE ISOQUINOLINE GROUP



Papaverine



Laudanosine
(*d* N-Methyl-tetrahydropapaverine)



Laudanine

[1] Attempts to synthesise strychnine derivatives have been made by Clemo, Perkin and Robinson, *J. C. S.*, 1924, 125, 1751.

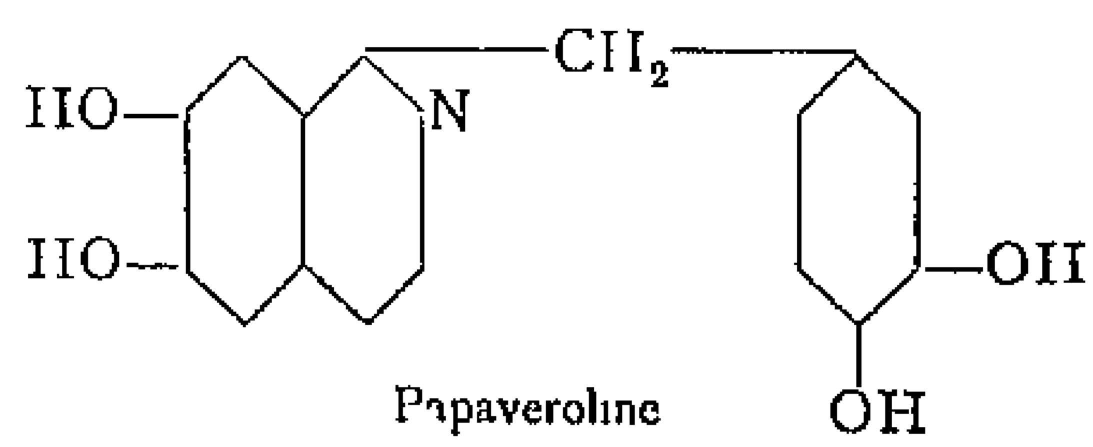
This group includes the five opium alkaloids, papaverine, laudanosine, laudanine, narcotine and narceine All these are known to be related to isoquinoline, the first three being comparatively simple derivatives

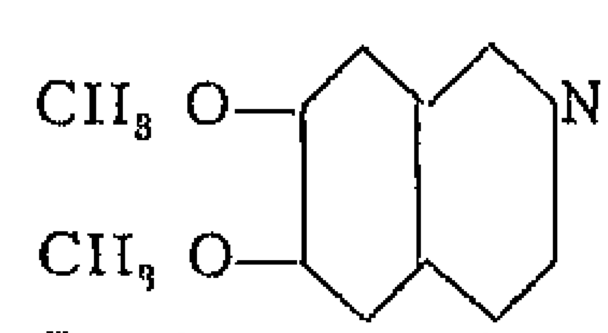
When it is remembered that the alkaloids hydrastine and berberine found in the root of *Hydrastis canadensis*, are also derived from isoquinoline, the importance of the latter as a parent compound of alkaloid bases becomes obvious

Papaverine, $C_{20}H_{21}NO_4$, occurs in opium in small quantities (0 8-1 0 per cent) and crystallises in prisms which melt at 147° It is almost insoluble in water or alkalis

The constitution of papaverine (see above) was established by G Goldschmiedt,[1] from an examination of the manner in which the compound is decomposed by halogen acids, potassium permanganate and fused alkali

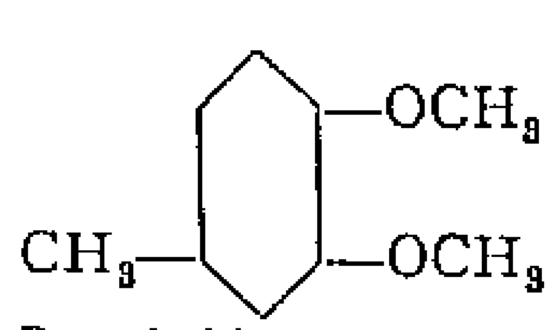
When the alkaloid is heated with hydriodic acid, four molecules of methyl iodide are liberated and *papaveroline* formed

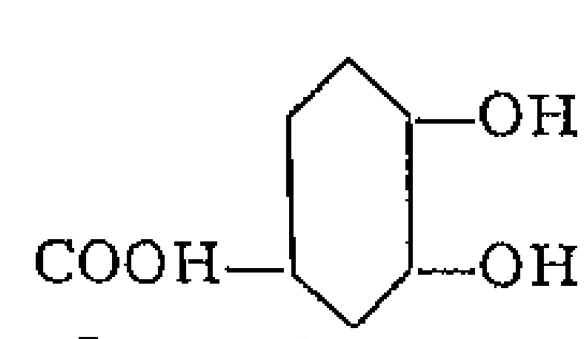

Papaveroline

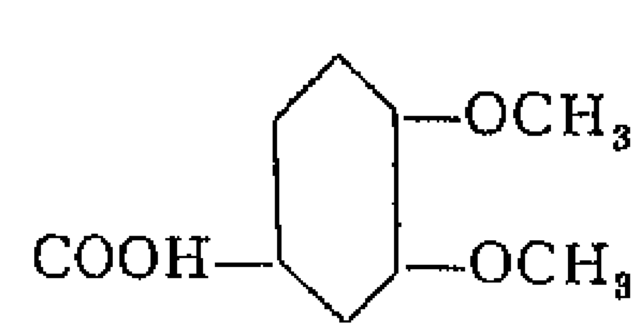

Dimethoxy isoquinoline

This reaction proves the presence of four methoxy groups in papaverine

Decomposition of Papaverine on Fusion with Alkali—When fused with potash, papaverine is decomposed into *dimethoxy-isoquinoline* and a compound which does not contain nitrogen The latter has been shown to be *dimethyl-homocatechol*, as it yields *protocatechuic acid* on more energetic treatment with potash In addition, an appreciable quantity of *veratric acid* is always produced during the oxidation of the alkaloid It will be observed that the side chains occupy the same positions in all these compounds


Dimethyl homocatechol


Protocatechuic acid


Veratric acid

[1] *Monats*, 1883 to 1889

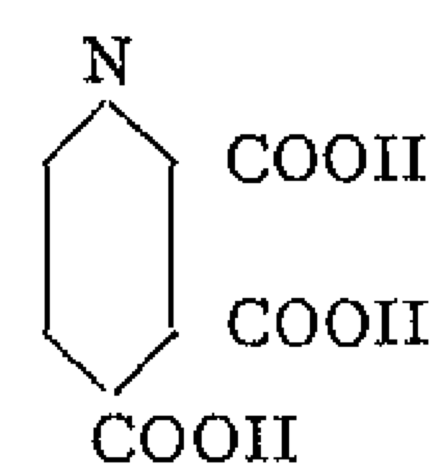
Constitution of Papaverine.—Papaverine can therefore be looked upon as a combination of dimethoxy isoquinoline and dimethyl-homocatechol

$$\underset{\text{Dimethoxy isoquinoline}}{C_{11}H_{11}NO_2} + \underset{\text{Dimethyl homocatechol}}{C_9H_{12}O_2} = \underset{\text{Papaverine}}{C_{20}H_{21}NO_4} + H_2$$

The manner in which these two components are joined together was determined by Goldschmiedt in the following way.

Papaverine contains four methoxy groups, two of which are contained in each of the above disruption products. Since the components cannot be united through the methoxy-groups, they must be joined through a carbon atom of the benzene nucleus, or of the methyl group of dimethyl-homocatechol. The latter supposition is supported by the whole behaviour of papaverine, especially the ease with which the component parts can be separated. Hence the alkaloid is a substituted *phenyl-isoquinoline-methane*.

Finally, it was necessary to determine which carbon atom of the isoquinoline ring takes part in the union. This point is decided by the fact that *when papaverine is oxidised with potassium permanganate, α-carbo-cinchomeronic-acid* (2, 3, 4-pyridine tricarboxylic acid) *is formed*.



α-Carbo cinchomeronic acid

Synthesis of Papaverine

The synthesis of papaverine was accomplished by A. Pictet[1] and Gams, by the reactions summarised in the table on p. 718.

By the reduction of papaverine methochloride with tin and hydrochloric acid, Pictet and Athanasescu[2] obtained the racemic form of N-methyl tetrahydro-papaverine. When this was resolved into its active components by means of quinic acid, the dextrorotatory enantiomorph proved to be identical with the alkaloid **laudanosine** occurring in opium. The constitution of this alkaloid is therefore that given on p. 715. The narcotic properties of papaverine are not very marked, but they appear to be altogether absent in laudanosine. A complete synthesis of laudanosine may be effected in a manner similar to that employed for papaverine.[3]

Laudanine, which occurs in very small quantities in opium, was first investigated by Hesse and Goldschmiedt. Its constitution was finally solved by Späth,[4] who determined the position of the free phenolic hydroxyl group. It has been synthesised by Späth and Lang[5] (formula, see p. 715).

[1] A. Pictet and A. Gams, *Ber.*, 1909, 42, 2943. See also K. W. Rosenmund, *Ber.*, 1927, 60, 392; E. Späth, *Ber.*, 1927, 60, 701. [2] Pictet and Athanasescu, *Ber.*, 1900, 33, 2346. [3] A. Pictet and M. Finkelstein, *Ber.*, 1909, 42, 1979. [4] Späth, *Monats.*, 1920, 41, 297. [5] Späth and Lang, *Monats.*, 1921, 42, 281.

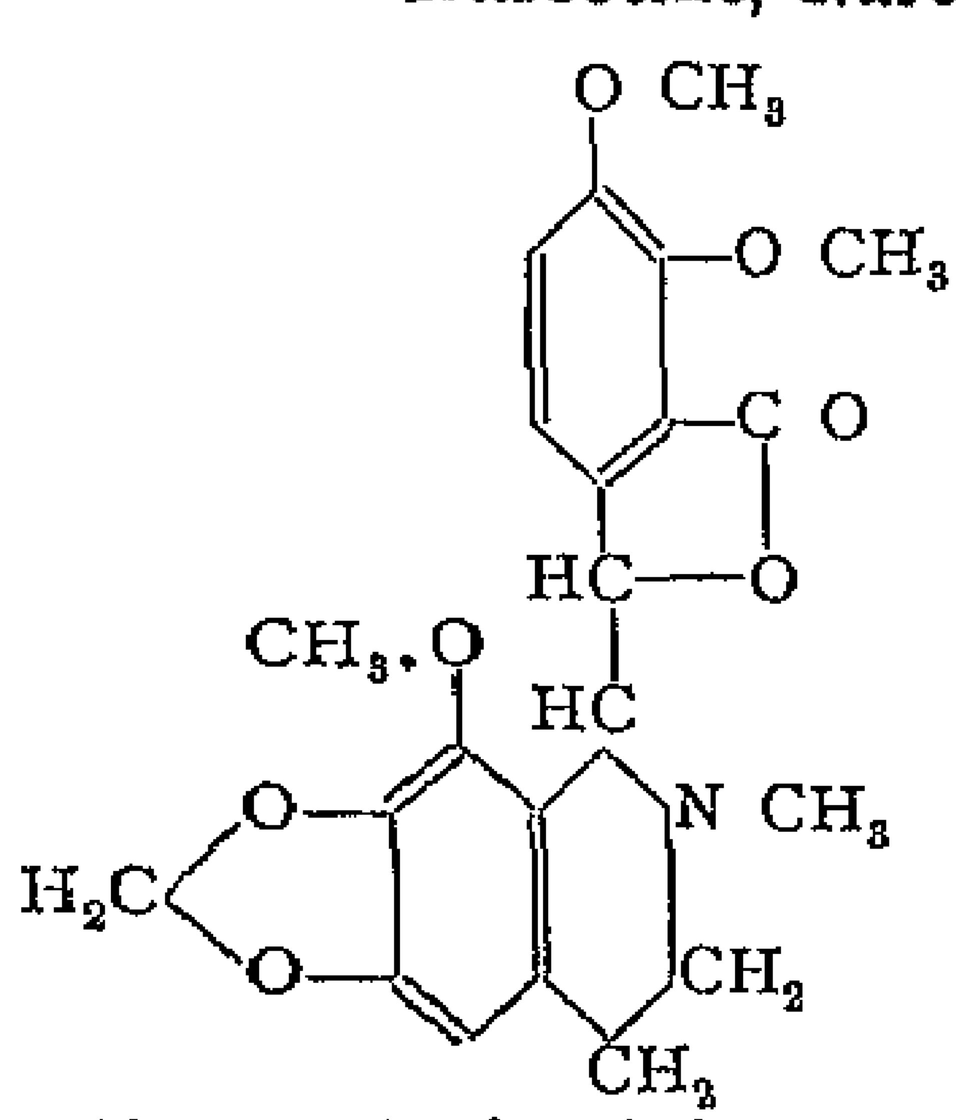
Synthesis of Papaverine

Veratrol
$(CH_3O)_2C_6H_4$
↓
Acetoveratrone
$(CH_3O)_2C_6H_3\ CO\ CH_3$
↓
Isonitroso-acetoveratrone
$(CH_3O)_2C_6H_3\ CO\ CH\ N\ OH$
↓
Amino-acetoveratrone hydrochloride
$(CH_3O)_2C_6H_3\ CO\ CH_2NH_3Cl$

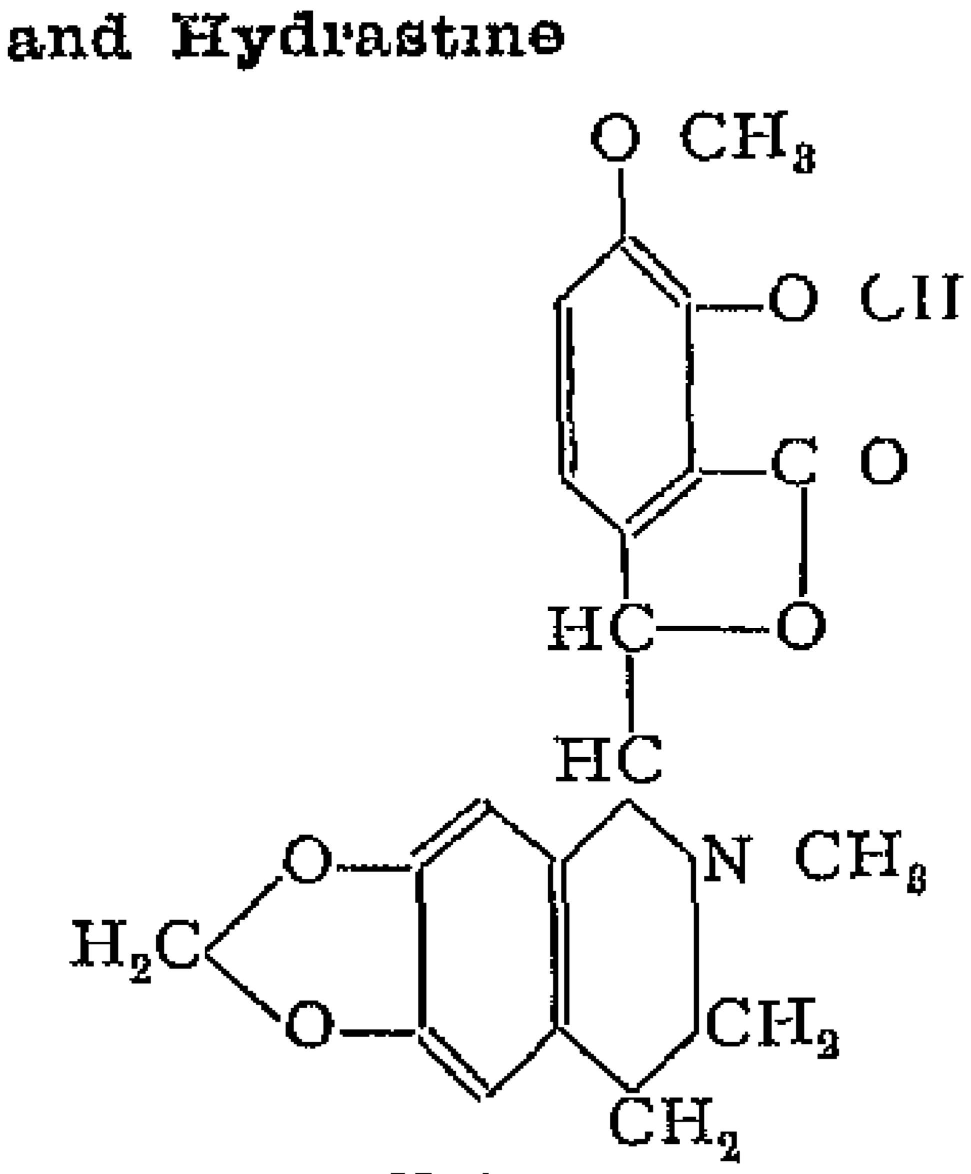
Vanillin
$(CH_3O)(OH)C_6H_3\ CHO$
↓
Methyl vanillin
$(CH_3O)_2C_6H_3\ CHO$
↓
Dimethoxy mandelo nitrile
$(CH_3O)_2C_6H_3\ CH(OH)\ CN$
$\downarrow$ HI
Homoprotocatechuic acid
$(OH)_2C_6H_3\ CH_2\ COOH$
↓
Homoveratric acid
$(CH_3O)_2C_6H_3\ CH_2\ COOH$
↓
Homoveratroyl chloride
$(CH_3O)_2C_6H_3\ CH_2\ COCl$

↓
Homoveratroyl amino-acetoveratrone
$(CH_3O)_2C_6H_3\ CO\ CH_2\ NH\ CO\ CH_2\ C_6H_3(OCH_3)_2$
↓
Homoveratroyl hydroxy homoveratryl amine
$(CH_3O)_2C_6H_3\ CH(OH)\ CH_2\ NH\ CO\ CH_2\ C_6H_3(OCH_3)_2$
$\downarrow$ P_2O_5
Papaverine
$(CH_3O)_2C_6H_2\ CH\ CH\ N\ C\ CH_2\ C_6H_3(OCH_3)_2$

Narcotine, Narceine and Hydrastine



Narcotine (methoxy-hydrastine)



Hydrastine

Narcotine, $C_{22}H_{23}NO_7$, is present as the free alkaloid in opium, in quantities varying from 0·75 to 9 per cent. After removing morphine and codeine from opium by extraction with water, narcotine is obtained by treating the residue with warm ether. It crystallises in rhombic prisms, m.p. 176°, and is insoluble in cold water or alkali. Narcotine is a *tertiary base*, and does not react with acetic anhydride. Hence the molecule contains *no free hydroxyl group*.

The presence of *three methoxyl groups* is shown by heating the alkaloid with hydrochloric acid, when it yields three molecular proportions of methyl chloride, together with *nornarcotine*, $C_{19}H_{17}NO_7$ or $C_{19}H_{11}NO_4(OH)_3$.

Narcotine is decomposed by potassium hydroxide at 220° with liberation of methylamine, dimethylamine and trimethylamine; the nitrogen atom is therefore attached to a methyl group.

Our knowledge of the constitution of narcotine is largely due to the work of Roser.[1]

Decomposition of Narcotine into Nitrogenous and Nitrogen-free Components

The decomposition of narcotine under the influence of reagents, such as water at 140°, dilute acids, and alkalis, has thrown valuable light on its constitution. Under this treatment it yields a nitrogen-free compound, *opianic acid*, and a base, *hydro-cotarnine*.

$$\underset{\text{Narcotine}}{C_{22}H_{23}NO_7} + H_2O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydro-cotarnine}}{C_{12}H_{15}NO_3}$$

With oxidising agents, *e.g.* nitric acid, platinic chloride, ferric chloride, or lead peroxide, narcotine decomposes in a similar manner to give *opianic acid* and *cotarnine*.

$$C_{22}H_{23}NO_7 + O + H_2O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine}}{C_{12}H_{15}NO_4}$$

Reducing agents such as zinc and hydrochloric acid, and sodium amalgam, convert narcotine into *meconine*, which is a reduction product of opianic acid, and *hydro-cotarnine*.

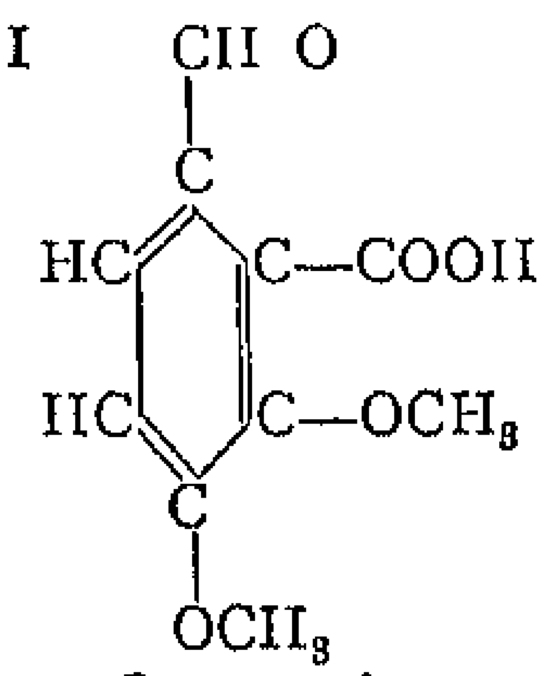
$$C_{22}H_{23}NO_7 + H_2 = \underset{\text{Meconine}}{C_{10}H_{10}O_4} + \underset{\text{Hydro-cotarnine}}{C_{12}H_{15}NO_3}$$

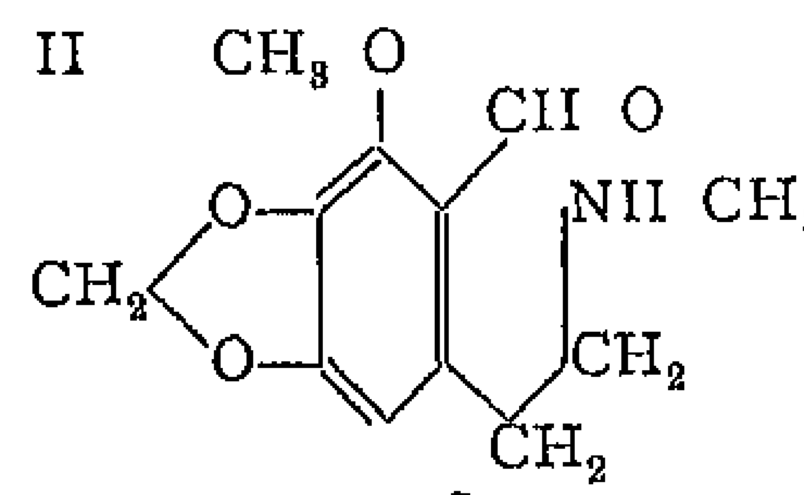
From these reactions it is evident that the molecule of narcotine consists essentially of two parts: a basic component corresponding to hydro-cotarnine, and a nitrogen-free substance corresponding to opianic acid.

Once the structure of these individual parts had been determined, it was possible to build up the formula of narcotine itself.

[1] Roser, *Ann.*, 1888, **245**, 311; **247**, 167; **249**, 156, 168; 1889, **254**, 334.

Opianic acid was investigated by Beckett and Wright,[1] and by Wegscheider, and proved to be a carboxylic acid derived from dimethyl-protocatechuic aldehyde Its constitution is represented by formula I

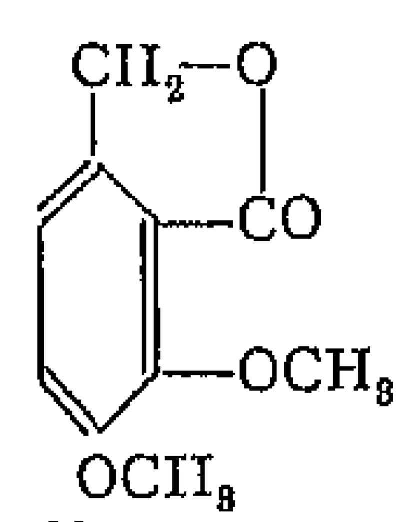
I 
Opianic acid

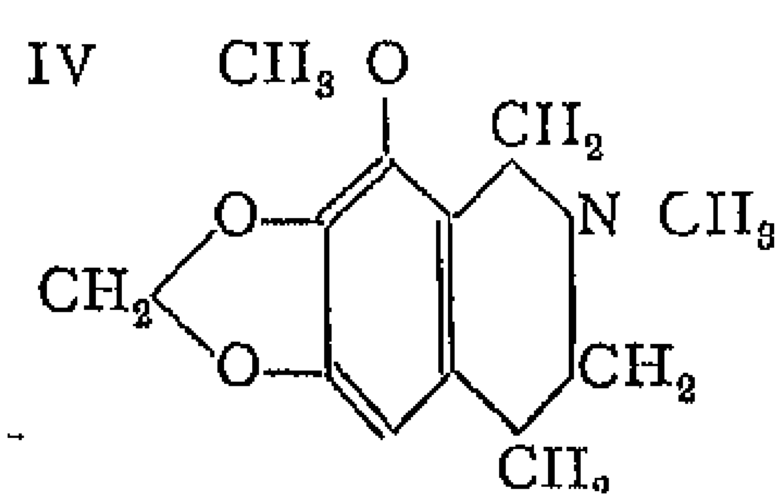
II 
Cotarnine

From a study of the products obtained by oxidation, and by interaction with methyl iodide, cotarnine has been assigned formula II (Roser) For an alternative formula see IV, p 721

Meconine, formula III, has been shown to be the lactone of the alcohol corresponding to opianic acid

The conversion of cotarnine into hydro-cotarnine, by means of reducing agents, takes place by reduction of the aldehyde group —CHO to —CH_2OH, followed by the formation of an isoquinoline ring by elimination of water between the groups —CH_2OH and —$NHCH_3$ Hydro-cotarnine is therefore assigned formula IV

III 
Meconine

IV 
Hydro cotarnine

The constitution of the decomposition products opianic acid or meconine on the one hand, and cotarnine or hydro-cotarnine on the other, is therefore clear The only point still to be decided is how the two component parts are linked together to form the alkaloid molecule

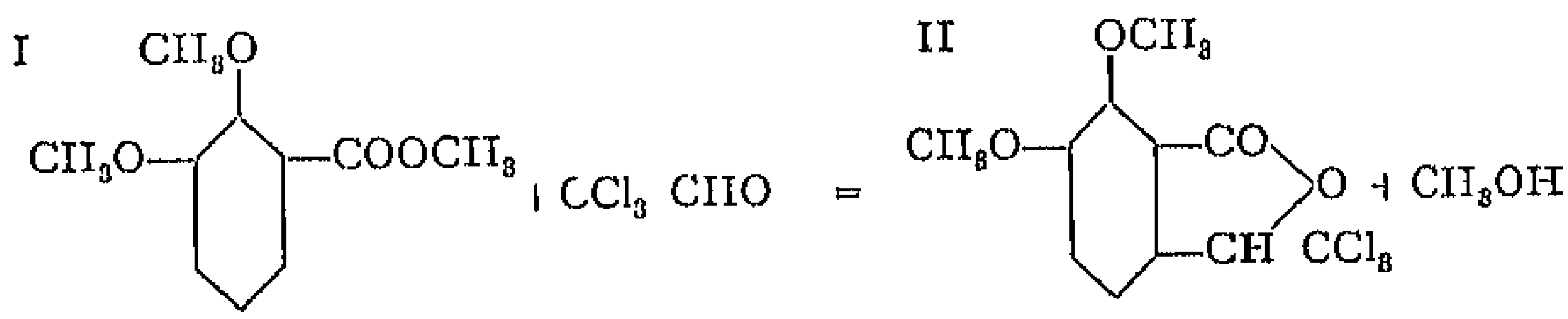
In narcotine, $C_{22}H_{23}NO_7$, the hydro-cotarnine group cannot be united with opianic acid or meconine through one of the seven oxygen atoms, since five of these are already joined to alkyl groups (three to methyl and two to methylene) and the other two are both present in a lactone ring Further, the valencies of the nitrogen atom are fully satisfied by the demands of the isoquinoline ring and the methyl group The

[1] Beckett and Wright, *J C S*, 1875, 28, 583

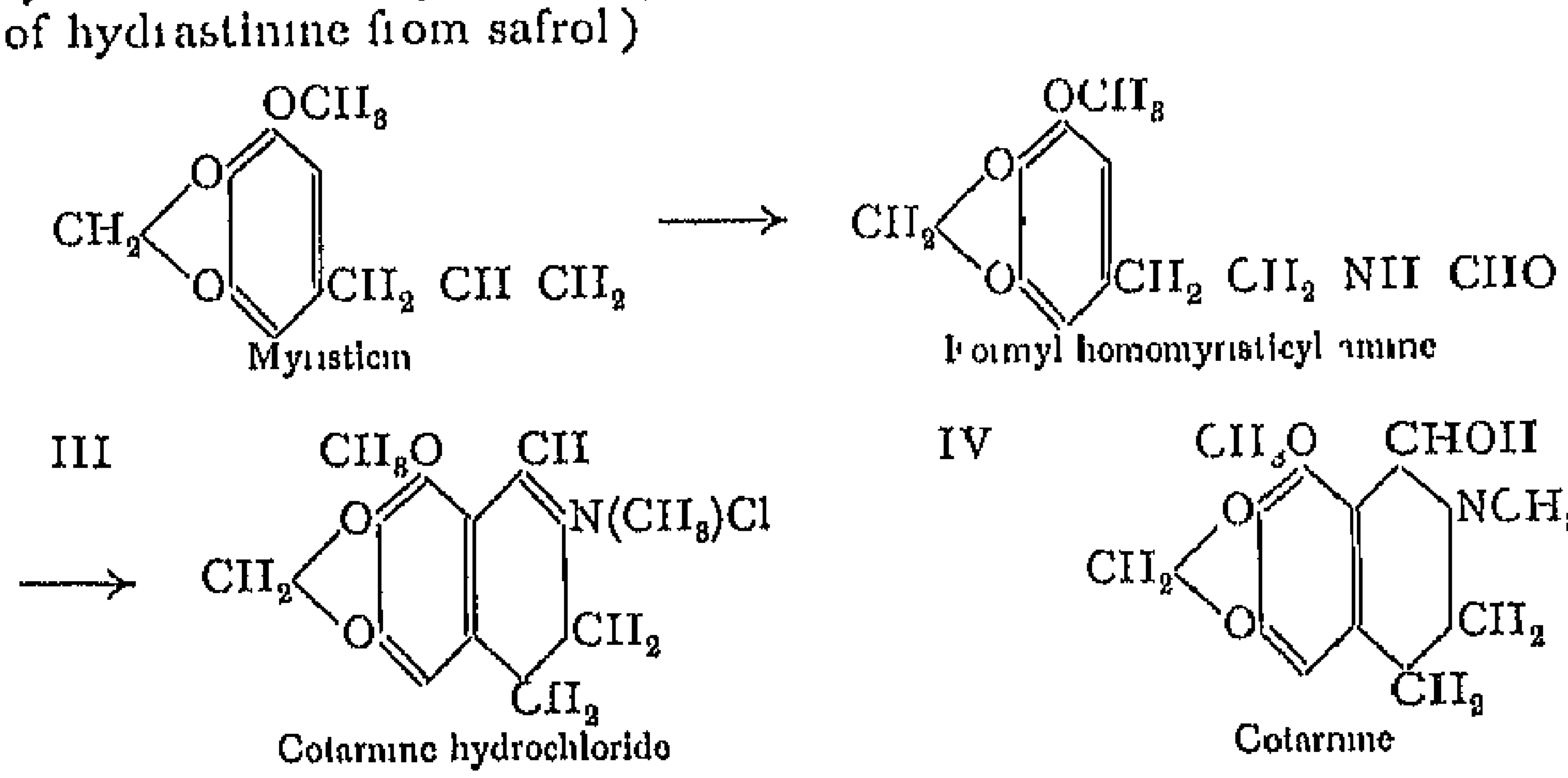
two components must therefore be connected through carbon atoms There is no doubt that it is these carbon atoms which take up oxygen during the oxidation of the alkaloid and appear as aldehyde groups in opianic acid and cotarnine, since no aldehyde group is present in narcotine itself For these reasons narcotine is given the constitution quoted on p 718

Synthesis of Narcotine—Perkin and Robinson[1] showed that when meconine and cotarnine are boiled in alcoholic solution with potassium carbonate a compound is produced which is identical with the racemic alkaloid *gnoscopine* By resolving this into its active components, *d*-and *l*-narcotine were obtained, the *l*-variety being identical with the natural alkaloid

Synthesis of Meconine[2]—Guaiacol carboxylic acid, on methylation, was converted into the methyl ester of 2 3-dimethoxy-benzoic acid, I The latter was condensed with chloral to give 5 6 dimethoxy-trichloro-methyl phthalide, II, which was then hydrolysed to the corresponding phthalide carboxylic acid The acid, on being heated, decomposed into carbon dioxide and meconine



Synthesis of Cotarnine—This base was synthesised by Salway, and later by Decker and Becker, from myristicin,[3] a constituent of oil of parsley and oil of nutmeg An intermediate product in the later synthesis was formyl-homomyristicyl-amine (Compare the preparation of hydrastinine from safrol)



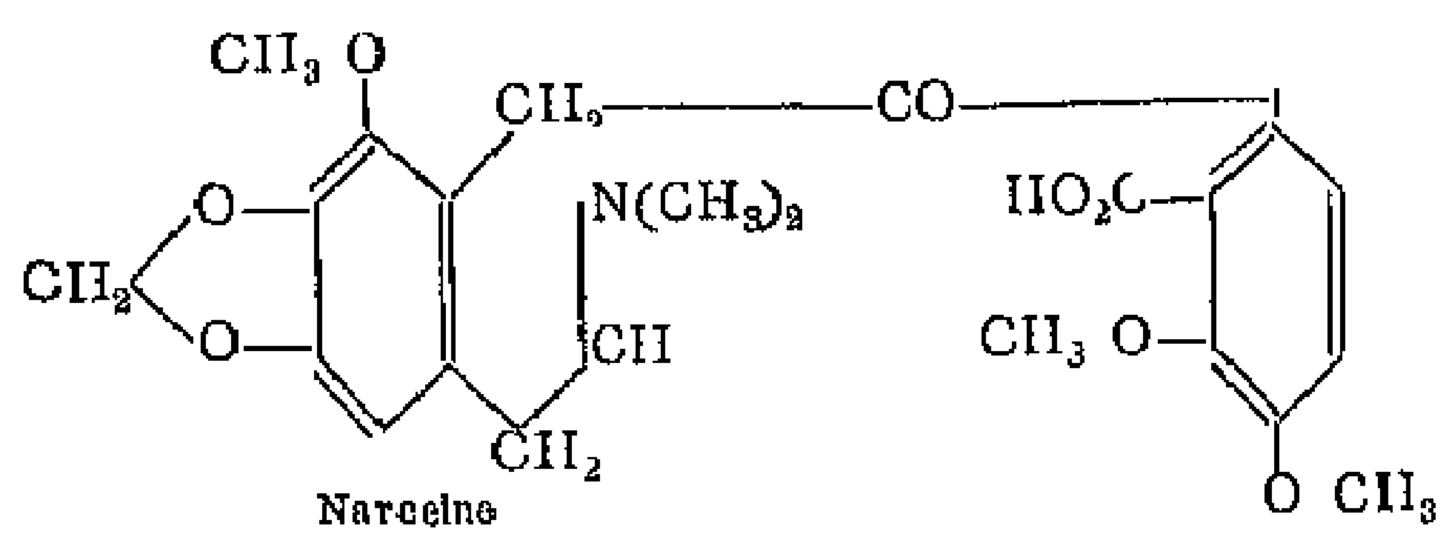
Myristicin — Formyl homomyristicyl amine

III Cotarnine hydrochloride — IV Cotarnine

[1] *Proc Chem Soc*, 1910, 26, 46, 131 [2] Fritsch, *Ann*, 1898, 301, 352 [3] Salway, *J C S*, 1910, 97, 1208 Decker and Becker, *Ann*, 1913, 396, 328

Spectroscopic investigations by Dobbie, Lauder and Tinkler [1] have shown that cotarnine salts correspond to the ammonium structure, III, but that the free base may exist either as the carbonium form, IV (in ether or chloroform solution), or as a mixture of the two forms (in aqueous or alcoholic solution)

Narceine is obtained by the action of alkali on narcotine methiodide It is present in opium in small quantities (about 0 1 per cent), and is a white crystalline compound of melting point 171° It has the following structure, and is formed from narcotine by the rupture of the pyridine and lactone rings



Narceine

Hydrastine (see formula on p 718) occurs in the root of *Hydrastis canadensis* L, a plant belonging to the Ranunculaceæ and indigenous to North America It crystallises in prisms, m p 135° The extract of *Hydrastis canadensis* is used therapeutically in cases of uterine hæmorrhage

The structure of hydrastine, which was established by the work of Freund [2] and E Schmidt,[3] is very similar to that of narcotine

When hydrastine is oxidised with potassium permanganate in acid solution, *opianic acid* is formed (Compare Narcotine, p 719)

On oxidation with dilute nitric acid at 50° to 60°, however, hydrastine yields, in addition to opianic acid, a basic compound of the formula $C_{11}H_{13}NO_3$, known as *hydrastinine*

$$\underset{\text{Hydrastine}}{C_{21}H_{21}NO_6} + H_2O + O = \underset{\text{Opianic acid}}{C_{10}H_{10}O_5} + \underset{\text{Hydrastinine}}{C_{11}H_{13}NO_3}$$

The difference of CH_2O between the molecules of cotarnine and hydrastinine, the basic decomposition products of narcotine and hydrastine respectively, indicates that cotarnine is a methoxy-hydrastinine Narcotine must therefore be a methoxy-hydrastine with the methoxyl group attached to the basic part of the molecule This conclusion has been confirmed by the determination of the methoxyl group by Zeisel's method (E Schmidt)

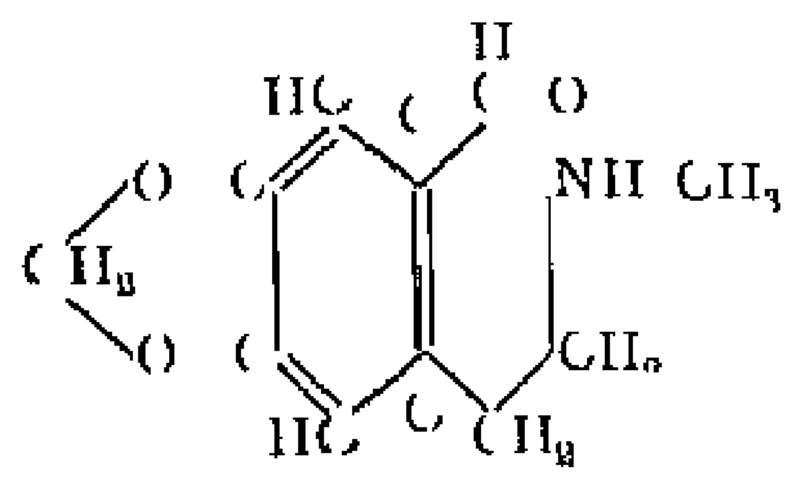
Hydrastinine is of the greatest importance in connection with the constitution of hydrastine Its structure has been ascertained both by degradation and synthesis

[1] Dobbie, Lauder and Tinkler, *J C S*, 1903, 83, 598, 1904, 85, 121 [2] M Freund, *Ann*, 1892, 271, 31. [3] E Schmidt, *Archiv der Pharm*, 1893, 231, 541

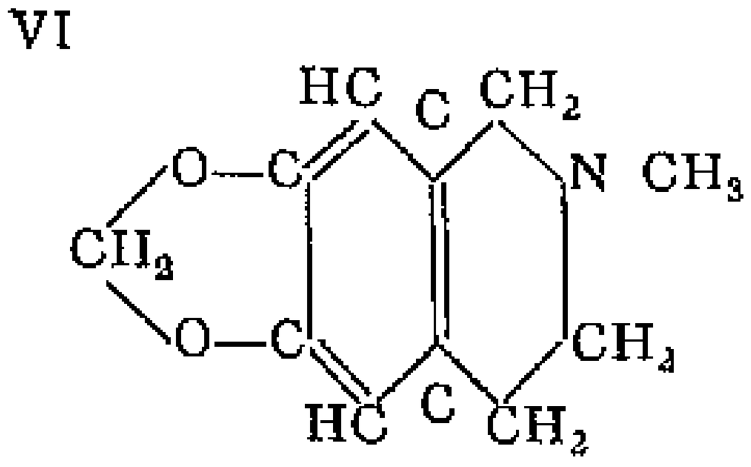
Synthesis of Hydrastinine

Hydrastinine (V.) is a derivative of piperonal, containing a basic side chain in the ortho position to the aldehyde group. When it is reduced with zinc and hydrochloric acid, ring formation takes place with loss of oxygen and production of hydro-hydrastinine (VI.). This compound is an isoquinoline derivative and formed an intermediate product in the first synthesis of hydrastinine to be effected.[1]

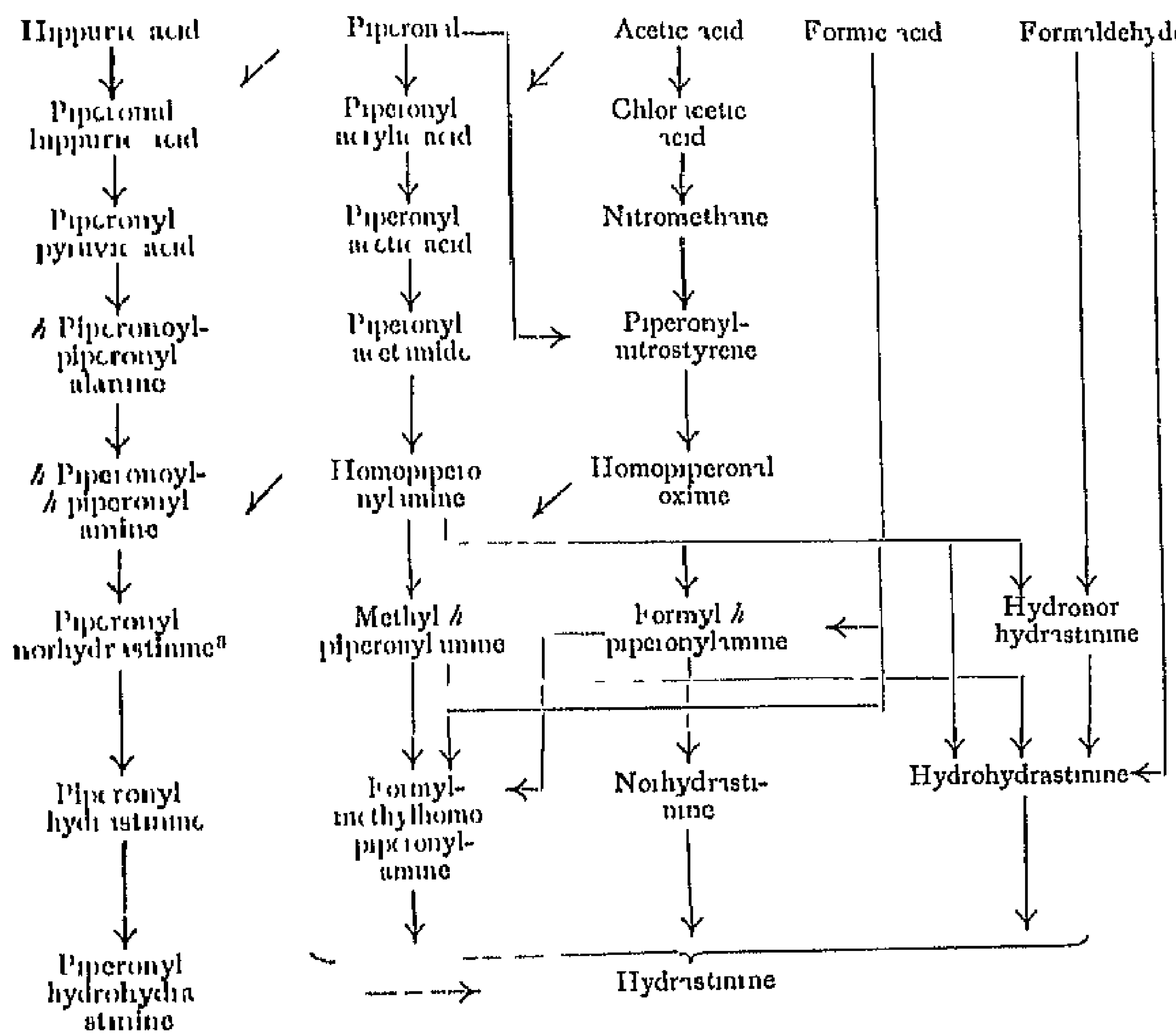
V



VI



Decker[2] has accomplished several syntheses of hydrastinine by reactions which are summarised in the following table:



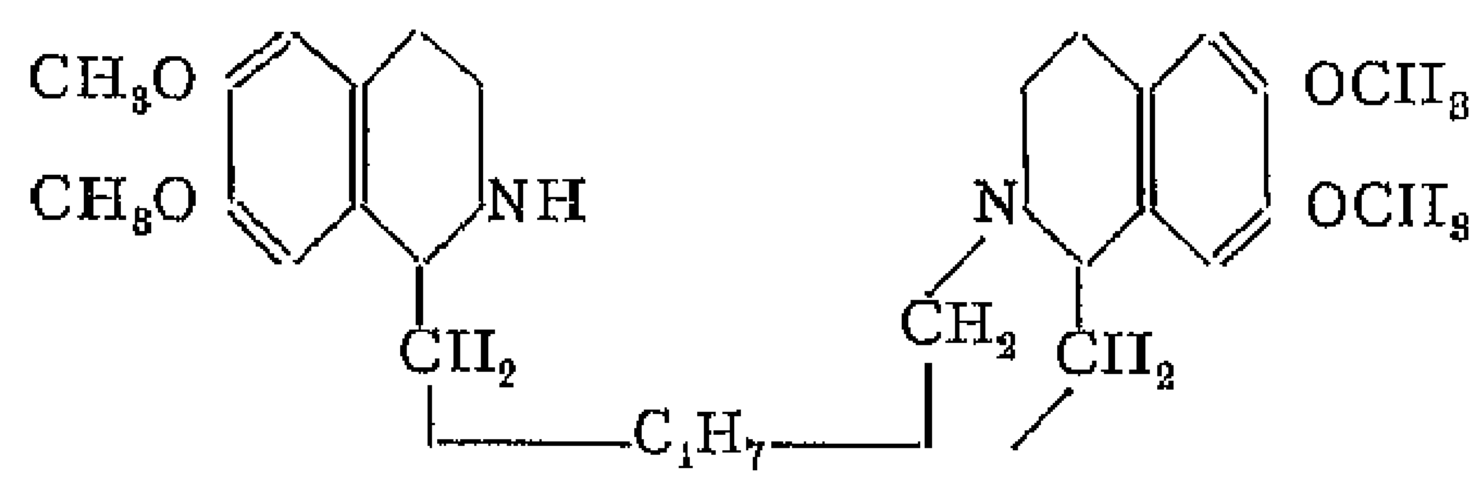
Emetine and Cephaleïn

Ipecacuanha has long been used medicinally as an emetic and purgative and also more recently in cases of amœbic dysentery. Pelletier in 1817 identified its most important active principle as the

[1] Fritsch, *Ann.*, 1895, 286, 18. [2] Decker, *Ann.*, 1913, 395, 321; see also Rosenmund, *J. C. S.*, 1919, A, i, 280. [3] See, however, Buck, Perkin and Stevens, *J. C. S.*, 1925, 127, 1462.

base *emetine* In addition, ipecacuanha contains *cephaelin*, psychotrine, *o*-methyl-psychotrine and emetamine, all of which stand in close relationship to one another[1] Within the last few years Späth[2] has partially elucidated the structure of emetine and cephaelin Emetine is an O-methyl-cephaelin, these two bases have thus similar constitutions

Emetine contains two 6 7-dimethoxy-1 2 3 4-tetrahydro-isoquinoline complexes and has been assigned the following skeleton formula by Späth

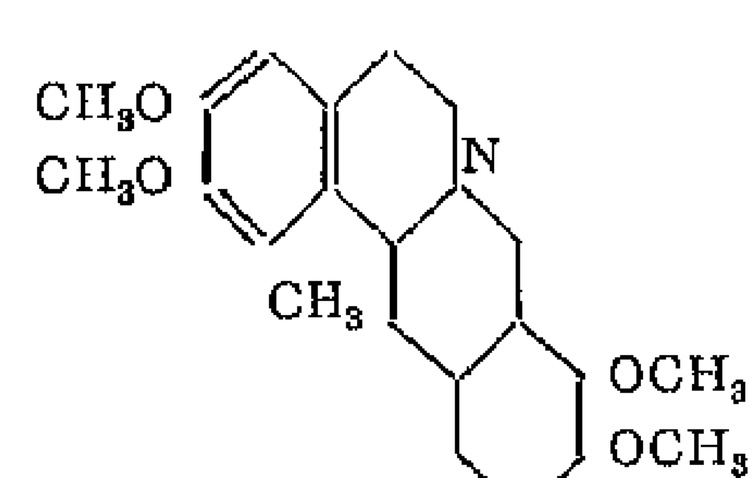


The structure of the residue C_4H_7 between the two cyclic groups is not yet determined

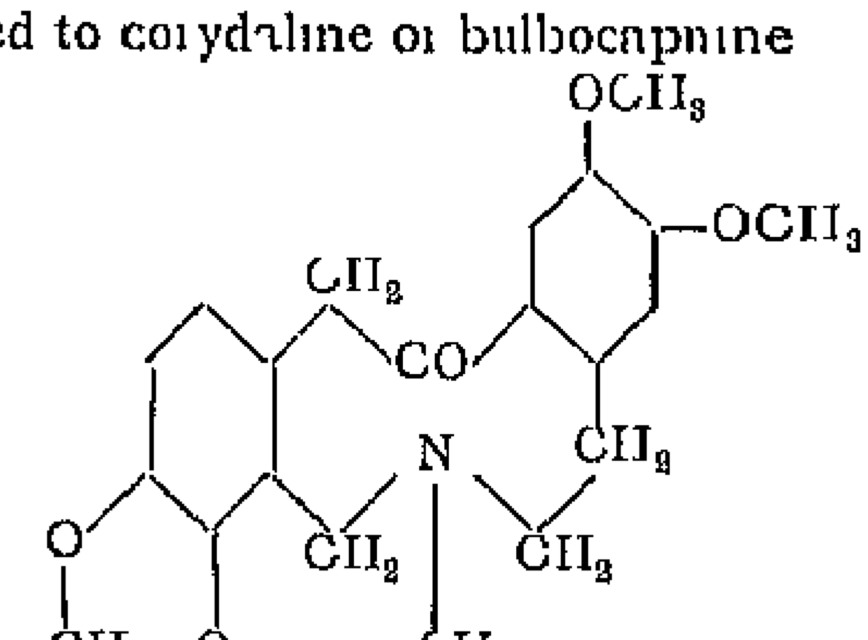
Cephaelin possesses a similar constitution to emetine, but has a phenolic hydroxyl in place of a methoxyl group

Corydalis Alkaloids

A large number of alkaloids are present in the bulbous rhizomes of *Corydalis cava*, belonging to the Papaveraceæ family, which in this respect is a worthy counterpart of *Papaver somniferum*, the source of the opium alkaloids At least fifteen alkaloids have been discovered in the corydalis group, our knowledge of them being chiefly due to Gadamer, who has subdivided them into the corydaline, bulbocapnine and corycavine groups The members of the corydaline group are closely related to hydroberberine, and those of the bulbocapnine group to apomorphine The latter undoubtedly contain a phenanthrene nucleus and must therefore be regarded as members of the phenanthrene group of alkaloids The constitution of the corycavine group is not known with sufficient certainty to show whether this group is directly related to corydaline or bulbocapnine



Corydaline



Cryptopine

The constitutions of cryptopine and protopine have been established by W H Perkin, jun, and co workers[3] By replacing the two methoxyl groups at the top right hand side of the above cryptopine formula by a methylene ether group ($O—CH_2—O$) the structure of protopine is obtained[3]

[1] For earlier references see Karrer, *Ber*, 1916, 49, 2058 [2] E Späth and W Leithe, *Ber*, 1927 60, 688 See also W H Brindley and F L Pyman, *J C S*, 1927, 1067 [3] R D Haworth and W H Perkin, jun, *J C S*, 1926, 1769 See also *Chem Soc Ann Rep*, 1926, 169, 187 *et seq*

Up to the present the following individual bases have been isolated

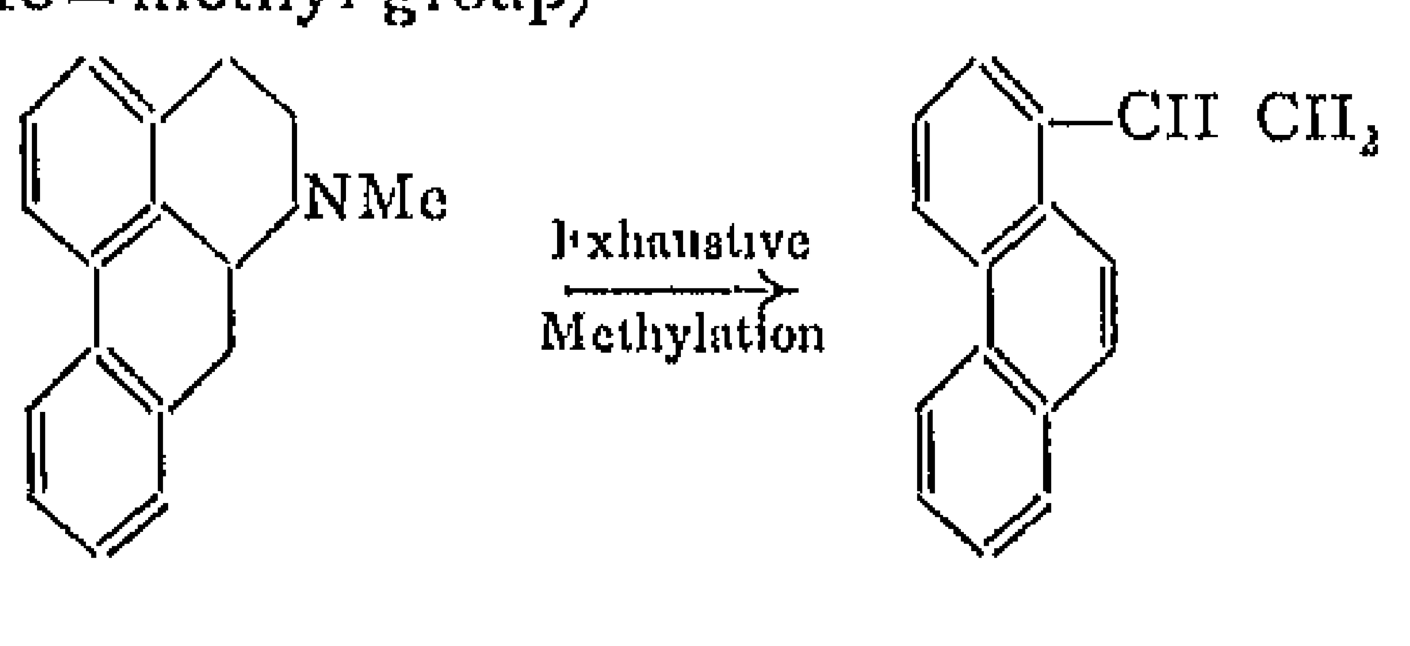
1	Corydaline	$C_{22}H_{27}NO_4$	9	Bulbocapnine	$C_{19}H_{19}NO_4$
2	Corybulbine	$C_{21}H_{25}NO_4$	10	Corydine	$C_{20}H_{23}NO_4$
3	Isocorybulbine	$C_{21}H_{25}NO_4$	11	Corypalmine	$C_{20}H_{23}NO_4$
4	Dehydrocorydaline	$C_{22}H_{24}NO_4 \cdot OH$	12	Corytuberine	$C_{19}H_{21}NO_4$
5	Corycavine	$C_{23}H_{23}NO_6$	13	Glaucine	$C_{21}H_{25}NO_4$
6	Corycavamine	$C_{21}H_{21}NO_5$	14		$C_{21}H_{21}NO_5$
7	Corycavidine	$C_{22}H_{25}NO_5$	15	Protopine	$C_{20}H_{19}NO_5$
8		$C_{20}H_{19}NO_5$			

Most of these alkaloids are similar to morphine in their physiological properties and effect on the heart, but as yet they are not used in medicine For information as to their constitution the original papers must be consulted [1]

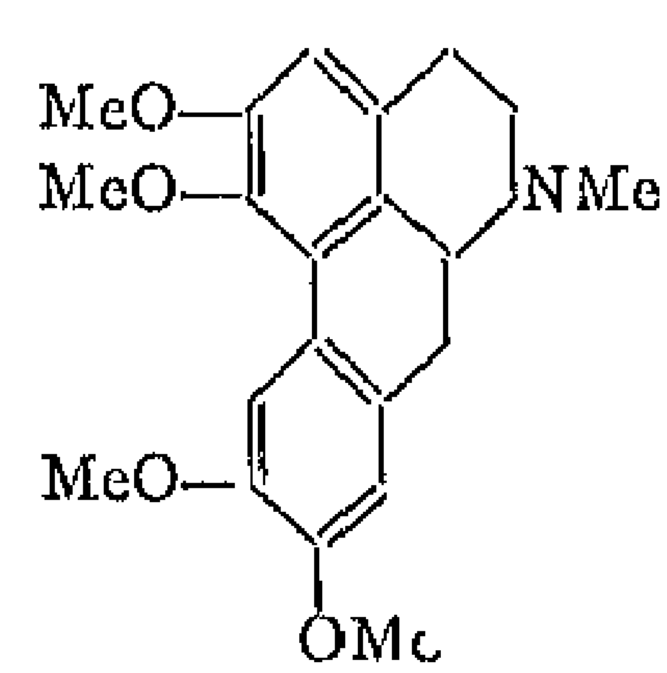
VI —ALKALOIDS OF THE PHENANTHRENE GROUP

Aporphine Group

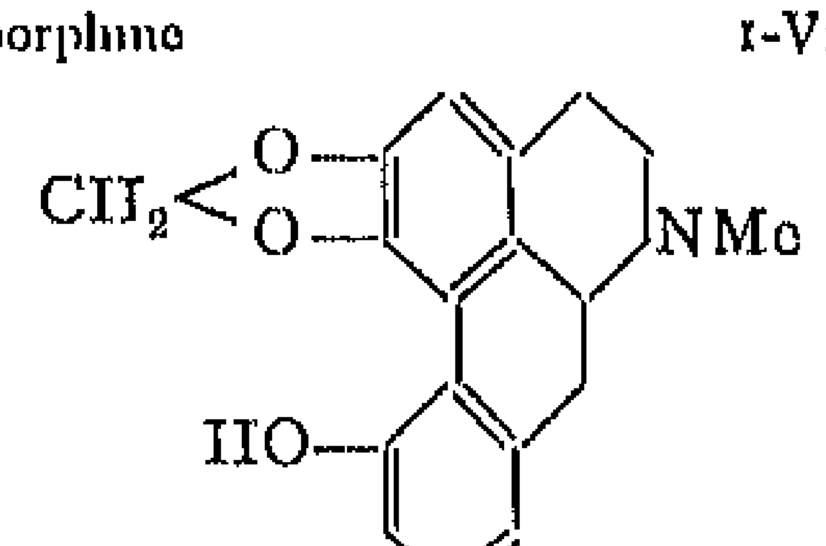
A number of the above-mentioned alkaloids, including glaucine, bulbocapnine and corytuberine are derivatives of aporphine, a base containing a condensed phenanthrene pyridine structure Glaucine and aporphine[2] have been synthesised by Gadamer, they are represented by the following abbreviated formulæ, in which the normal benzenoid nuclei are to be distinguished from the hydrogenated rings (Me = methyl group)



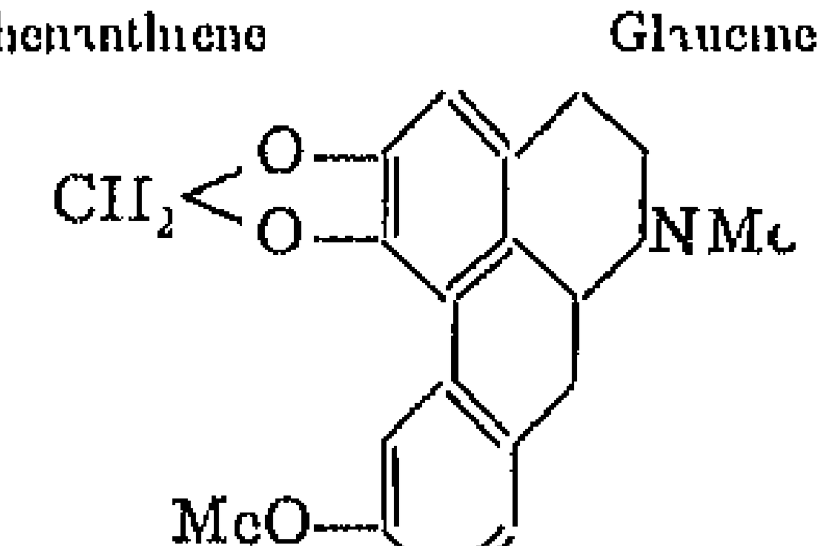
Aporphine 1-Vinyl phenanthrene



Glaucine



Pukateine



Laureline

Barger and his co-workers have established further examples of this type in laurotetanine[3] (from various Lauraceæ) and in pukateine and laureline[4] (from the bark of the Pukatea, Laurelia Novæ

[1] Gadamer, *Arch d Pharm*, 1902, 240, 19, 51, 1911, 249, 423, 487, 518, 1916, 254, 295 Feist, *ibid*, 1908, 245, 586, Asahina, *ibid*, 1909, 247, 202 E Späth and Lang, *Ber*, 1921, 54, 3074 [2] *Arch Pharm*, 1925, 263, 81 [3] G Barger and Silberschmidt, *J C S*, 1928, 2919 [4] G Barger and A Girardet, *Helv Chim Acta*, 1931, 481

Zealandiæ) From their general properties and behaviour on oxidation the last two compounds have been assigned the above constitutions In physiological action they resemble morphine

When submitted to exhaustive methylation apomorphine yields 1-vinyl-phenanthrene The methoxyl derivatives under similar treatment are converted into the corresponding 1-vinyl-methoxy-phenanthrenes

Morphine Alkaloids

Morphine, Codeine and Thebaine

It has been definitely proved that the alkaloids morphine, codeine and thebaine contain a phenanthrene nucleus, but the nature of the nitrogen ring is not yet known with certainty The idea originally advanced by Knorr, that they are derived from morpholine (p 238), has now been abandoned From the investigations of Pschorr it is probable that these compounds, like those in the previous section, contain an isoquinoline ring, but other possibilities are not excluded Hence the usual method of classification, according to the basic complex present, cannot be adopted here

Morphine is the chief basic constituent of opium, in which it is present in quantities varying from 3 to 23 per cent It was the first alkaloid to be isolated from a plant source, and its discovery by the apothecary Sertürner, in 1806, has been of great value to pharmacology and the development of organic chemistry Its composition was shown by Laurent to correspond to the formula $C_{17}H_{19}NO_3 + H_2O$

Morphine crystallises from alcohol in small prisms which melt with decomposition at 230° It dissolves sparingly in water, is odourless, has a bitter taste and is laevorotatory

The hydrochloride, $C_{17}H_{19}NO_3, HCl + 3H_2O$, *morphinæ hydrochloricum*, crystallises in fine silky needles It is widely used as a soporific and for the alleviation of pain Solutions of morphine and its salts give a dark blue coloration with ferric chloride, a solution of the alkaloid in concentrated sulphuric acid is coloured blood-red on the addition of a little nitric acid

Codeine also occurs in opium, but in smaller quantities (0 3 to 2 per cent) than morphine From this source it was isolated by Robiquet in 1832 Gerhardt proved the formula of codeine to be $C_{18}H_{21}NO_3,H_2O$, from which it was concluded to be a homologue of morphine It is generally prepared from the latter compound

Codeine crystallises in prisms or in octahedra of the rhombic system, it melts at 153° and is sparingly soluble in water or alkalis It is laevorotatory, very poisonous and possesses a somewhat bitter taste Like morphine it is a narcotic Codeine and similarly constituted compounds are of greater medicinal value than morphine, on account of their sedative action and the fact that they reduce

irritation of the air passages; hence they exert a favourable influence on respiration. Codeine is therefore a valuable specific in the treatment of coughs. Codeine methobromide is used under the name of *eucodine*.[1]

Thebaine, which crystallises in silvery plates of melting-point 193°, is present in opium in quantities varying from 0.2 to 1 per cent.

A comparison of the formulæ of morphine, codeine and thebaine suggests that these compounds are closely related to one another. This is supported by the common occurrence of the three bases in opium, and by the results of experimental investigation.

$$\underset{\text{Morphine}}{C_{17}H_{19}NO_3} \qquad \underset{\text{Codeine}}{C_{18}H_{21}NO_3} \qquad \underset{\text{Thebaine}}{C_{19}H_{21}NO_3}$$

For this reason it is convenient to discuss morphine, codeine and thebaine in connection with one another. Owing to their greater practical importance, morphine and codeine will be treated in more detail.

Action of Dehydrating Agents on Morphine

Oxalic acid, sulphuric acid, hydrochloric acid, phosphoric acid, alkalis and concentrated solutions of zinc chloride may act on morphine in two ways. Sometimes condensation takes place with the formation of compounds such as *trimorphine* and *tetramorphine*, and sometimes water is eliminated according to the equation:

$$\underset{\text{Morphine}}{C_{17}H_{19}NO_3} = H_2O + \underset{\text{Apomorphine}}{C_{17}H_{17}NO_2}$$

The compound **apomorphine** is an amorphous, sparingly soluble base, which readily undergoes oxidation. In physiological action it differs entirely from morphine; it has no narcotic properties but is a powerful emetic. For its constitution, see p. 736.

Functions of the three Oxygen Atoms in Morphine. Relationship of Morphine to Codeine

The three oxygen atoms of morphine possess different functions. One of them is present in a phenolic hydroxyl group, which endows the alkaloid with certain acidic properties. The hydrogen of this group is replaceable by metals and by acyl and alkyl radicals; in codeine it is replaced by a methyl group.

Codeine is therefore a methyl ether of morphine. This relationship between the two alkaloids was recognised by Matthiessen and Wright in 1869,[2] and represented by them as follows:—

$$\underset{\text{Morphine}}{C_{17}H_{17}NO(OH)_2} \qquad \underset{\text{Codeine}}{C_{17}H_{17}NO(OH)(OCH_3)}$$

By the action of concentrated hydrochloric acid on codeine at 100° they obtained an amorphous chlorinated derivative, *chlorocodide*:

$$\underset{\text{Codeine}}{C_{18}H_{21}NO_3} + HCl = \underset{\text{Chlorocodide}}{C_{18}H_{20}ClNO_2} + H_2O$$

[1] *C.*, 1905, II, 785. [2] *Proc. Roy. Soc.*, 1869, 17, 364.

When this was heated with water at 130°, codeine was regenerated. With hydrochloric acid at 150°, on the other hand, it was decomposed into apomorphine and methyl chloride:

$$\underset{\text{Chlorocodide}}{C_{18}H_{20}ClNO_2} = \underset{\text{Apomorphine}}{C_{17}H_{17}NO_2} + CH_3Cl$$

On combining these two equations, it is seen that hydrochloric acid decomposes codeine at 150° with elimination of a methyl group and a molecule of water. The solid reaction product is identical with that which results from morphine by the action of dehydrating agents. Hence codeine must be derived from morphine by the replacement of a hydroxyl group by a methoxyl group.

The conversion of morphine into codeine, which was effected in 1881 by Grimaux, confirmed the conclusions of Matthiessen and Wright, and definitely proved that codeine was the monomethyl ether of morphine. Grimaux prepared codeine from morphine by treating the latter with methyl iodide in the presence of alkali:

$$\underset{\text{Morphine}}{C_{17}H_{17}NO(OH)_2} + CH_3I + KOH = KI + H_2O + \underset{\text{Codeine}}{C_{17}H_{17}NO(OH)(OCH_3)}$$

The constitutions of these two alkaloids may thus be discussed together.

The *second oxygen atom in morphine* has been shown by Hesse to be present in an alcoholic grouping $>CH \cdot OH$, since codeine on oxidation yields a ketone *codeinone*.

The *third oxygen atom* is very non-reactive. According to Vongerichten,[1] it is united to two carbon atoms, as in the ethers $>C-O-C<$.

Roser and Howard, by the use of Zeisel's method, proved that *thebaine* contains two methoxyl groups. Thus the relationship between the three alkaloids may be represented as follows:—

				Non-reactive oxygen	Phenolic hydroxyl	Alcoholic hydroxyl
Morphine	C_{17}	H_{16}	N	O	OH	HOH
Codeine	C_{17}	H_{16}	N	O	OCH_3	HOH
Thebaine	C_{17}	H_{14}	N	O	OCH_3	$HOCH_3$

Function of the Nitrogen Atom in Morphine

The behaviour of morphine on *exhaustive methylation*[2] shows that the nitrogen atom is contained in a ring, and that it is attached to three carbon atoms and therefore tertiary. Morphine unites directly with one molecule of methyl iodide to give a methiodide.

When methyl-morphine methiodide (*i.e.*, codeine methiodide) is

[1] *Ann.*, 1881, 210, 105. [2] Knorr, *Ber.*, 1889, 22, 182.

heated with caustic soda it is readily converted into a tertiary base, **methyl-morphimethine** (Hesse)

$$C_{17}H_{17}O(OH)(OCH_3)\;N\begin{matrix}\diagup CH_3\\ \diagdown OH\end{matrix} = H_2O + C_{17}H_{16}O(OH)(OCH_3)\;N\;CH_3$$

This reaction resembles the transformation of dimethyl-piperidinium hydroxide into pentenyl-dimethylamine (see p 647 *et seq*), which necessarily involves the disruption of the piperidine ring Hence it may be concluded that the formation of methyl-morphimethine is due to the rupture of the nitrogen ring of morphine

Methyl-morphimethine exists in different isomeric forms and is a tertiary base, reacting only with one molecule of methyl iodide, to give a methiodide[1] Its constitution will be discussed more fully later

Thebaine is also a tertiary base and yields a methiodide of the formula $C_{19}H_{21}NO_3,CH_3I$

Arrangement of the Carbon Atoms in Morphine

Of the 17 carbon atoms in the morphine molecule, 14 must belong to a phenanthrene nucleus, since the non-nitrogenous decomposition products of the alkaloid have always proved to be phenanthrene derivatives

Phenanthrene itself was isolated by Schrotter and Vongerichten by the distillation of the alkaloid with zinc dust Knorr obtained it in the same way from methyl-morphimethine

Decomposition of Morphine, Codeine and Thebaine

The decomposition of morphine and its derivatives into nitrogenous compounds of low carbon content and nitrogen-free compounds, which are rich in carbon, may be accomplished in various ways, *e g*, 1 By the action of hydrochloric acid or acetic anhydride on the methohydroxides of morphine and codeine, or on methyl-morphimethine 2 By decomposition of the ammonium bases of the morphine group under the influence of heat or alkalis

Decomposition Products of Morphine which do not contain Nitrogen

The degradation products obtained by method 1 are derivatives of the compound *morphol*, $C_{14}H_8(OH)_2$, described on pp 552, 554, those obtained by method 2 are derived from the phenolic compound *morphenol*, see pp 552, 554

The constitution of these two compounds has been established chiefly through the analytical researches of Vongerichten and the syntheses of Pschorr

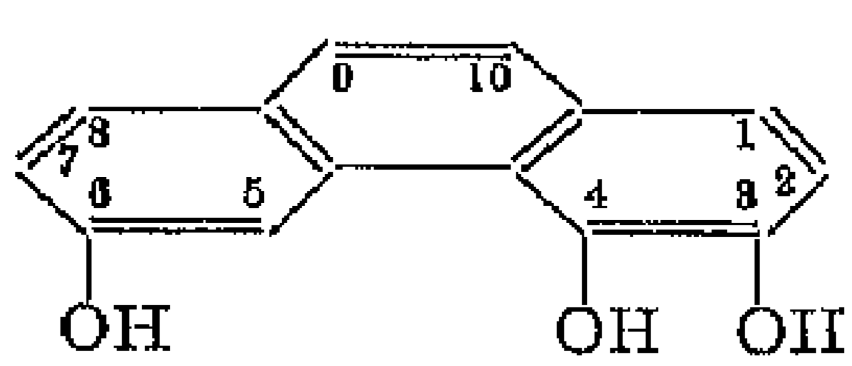
Morphol has been identified as 3 4-dihydroxy-phenanthrene, and

[1] Knorr, *Ber*, 1902, 35, 3012.

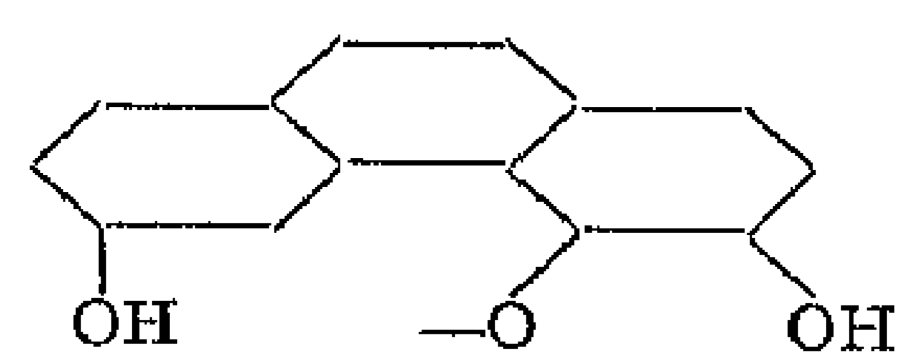
this constitution has recently been confirmed by the synthesis carried out by Barger[1] (p 552)

Pschorr and Vogtherr[2] prepared the acetyl derivative of 3-methoxy-4-hydroxy-phenanthraquinone by method 5 described on p 548, and found it to be identical with the acetyl derivative of methyl-morpholquinone which Vongerichten had previously obtained by heating methyl-morphimethine with acetic anhydride

Thus the methoxyl group in codeine and the phenolic hydroxyl group in morphine each occupy position 3 in the phenanthrene nucleus The further question as to whether the hydroxyl group in position 4 in the decomposition products corresponds to the indifferent oxygen atom or to the alcoholic hydroxyl of morphine was decided by Knorr[3] in favour of the former assumption He was able to show that one of the decomposition products of codeinone—a ketone obtained by the oxidation of codeine—is 3-methoxy-4 6 dihydroxy-phenanthrene, and concluded that the alcoholic hydroxyl group is attached to



position 6 Hence the alkaloids morphine and codeine are derivatives of 3 4 6-trihydroxy-phenanthrene From the investigations of thebaol and codeinone to be described later, it also follows that thebaine is derived from the same compound The functions of the three oxygen atoms in morphine may thus be indicated as follows,—



Alcoholic hydroxyl | Indifferent oxygen | Phenolic hydroxyl

Nitrogenous Decomposition Products of Morphine and the Decomposition Products of Thebaine

Our knowledge of the nitrogenous decomposition products of morphine is chiefly due to the investigations of Knorr[4]

The decomposition of methyl-morphimethine has given results of such importance that this compound may be considered the key to the constitution of morphine

By the decomposition of methyl-morphimethine metho-hydroxide under the influence of heat, the volatile basic decomposition product was found to be trimethylamine When treated with acetic anhydride the compound gave dimethylamine Hence, of the three carbon atoms

[1] Barger, *J C S*, 1918, 113, 218 [2] *Ber*, 1902, 35, 4412 [3] Knorr, *Ber*, 1903, 36, 3074
[4] Knorr, *Ber*, 1889, 22, 181, 1113, 2081, *Ber*, 1894, 27, 1144, *Ber*, 1904, 37, 3494, 3499, *Ber*, 1905, 38, 3172

which lie outside the phenanthrene nucleus in morphine, one must be united to nitrogen in the form of a methyl group.

Methyl-morphimethine was found to be decomposed by acetic anhydride to give the basic products *dimethylamine* and the acetyl derivative of *hydroxy-ethyl-dimethylamine*, $HO \cdot CH_2 \cdot CH_2 \cdot N(CH_3)_2$.

The isolation of hydroxyethyl-dimethylamine gave rise to the erroneous conclusion that in methyl-morphimethine the phenanthrene component and hydroxyethyl-dimethylamine are linked together through the oxygen atom of the base, and led Knorr to advance the "oxazine" or "morpholine formula" for morphine (see p. 732).

From thebaine, in a similar manner, Freund[1] obtained *acetoxyethyl-methylamine*, $CH_3CO \cdot O \cdot CH_2 \cdot CH_2 \cdot NH \cdot CH_3$, and acetyl-thebaol. The latter was identified by Pschorr[2] as 3 : 6-dimethoxy-4-acetoxy-phenanthrene (see p. 555), thus proving that the two methoxy groups in thebaol, and therefore also in thebaine, occupy positions 3 and 6.

In an attempt to isolate any intermediate compound which might be formed during this decomposition, Pschorr and Haas[3] investigated the action of benzoyl chloride on thebaine at 0°. The degradation of the alkaloid was found to take place very smoothly under such conditions, with the formation of the *benzoyl derivatives of thebaol* and *hydroxyethyl-methylamine*.

The above oxazine or morpholine formula had to be abandoned after the discovery that the complex C . C . N could be detached from the morphine molecule as *ethyl dimethylaminoethyl ether*,

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!N \cdot CH_2 \cdot CH_2 \cdot O \cdot C_2H_5,$$

by heating methyl-morphimethine with sodium methoxide, or thebaine and codeinone methiodides with alcohol.

The above ether-base, however, is not a primary decomposition product. Knorr suggests that the three-membered chain of the side ring is first removed from the morphine alkaloids in the form of an unsaturated compound, probably as *vinyl-dimethylamine* $(CH_3)_2N \cdot CH : CH_2$, which at once combines with alcohol to give the ether-base.[4]

$$(CH_3)_2N \cdot CH : CH_2 + C_2H_5OH = (CH_3)_2N \cdot CH_2 \cdot CH_2 \cdot O \cdot C_2H_5$$

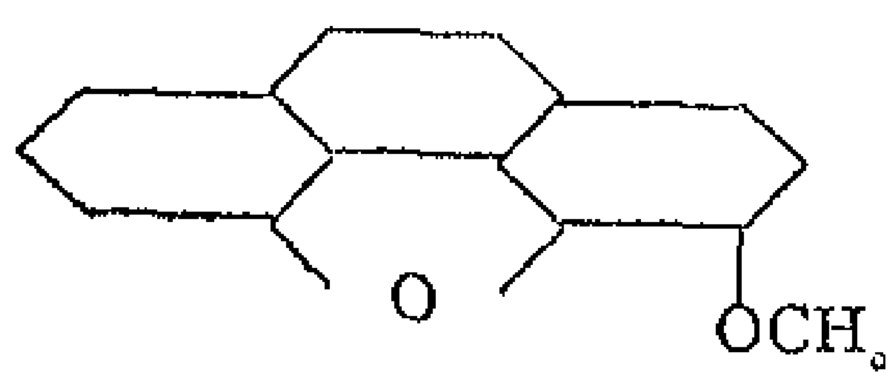
Should this prove correct, then the acetyl derivatives of the alcohol bases, obtained by the action of acetic anhydride on methyl-morphimethine, thebaine and codeine, must be regarded as secondary addition products of acetic acid with a compound which does not contain oxygen. In this case the formation of the hydramines cannot be due, as was formerly suggested, to a hydrolytic decomposition in which the

[1] Freund, *Ber.*, 1897, 30, 1357. [2] Pschorr, *Ber.*, 1902, 35, 4401. [3] Pschorr and Haas, *Ber.*, 1906, 39, 16. [4] L. Knorr, *Ber.*, 1904, 37, 3500, 3507.

"indifferent" oxygen of the original alkaloid is converted into the hydroxyl group of the alcohol base

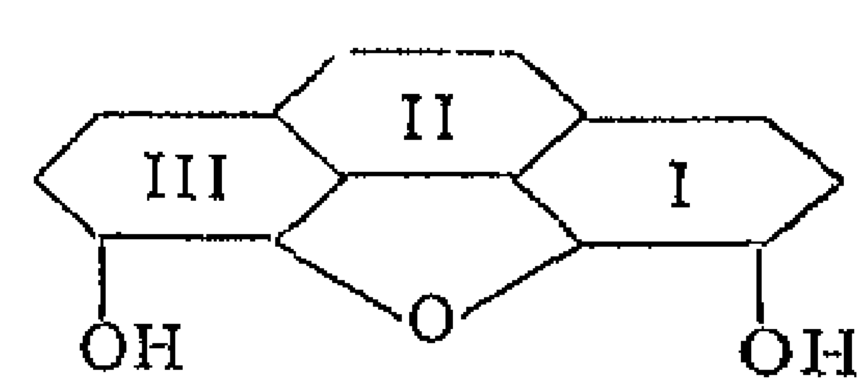
These views have received support from the observations of Knorr and Pschorr, who found that thebainone[1] is decomposed by acetic anhydride with the formation of hydroxyethyl-dimethylamine, thus behaving similarly to methyl-morphimethine, even though it no longer contains an indifferent oxygen atom

For these reasons the assumption of an oxazine ring in morphine and thebaine has proved untenable, and there is no doubt that the indifferent oxygen atom in the morphine alkaloids is present in a furane ring, forming a bridge between positions 4 and 5 of the phenanthrene nucleus A similar structure is found in methyl-morphenol, which is a decomposition product of methyl-morphimethine (Vongerichten) *The complex* $>(C_2H_4NCH_3)$ *is therefore attached to the phenanthrene nucleus in methyl-morphimethine and the morphine alkaloids by means of a carbon linking*



The same conclusion was arrived at by Freund[2] from a study of the *action of organo-magnesium halides on thebaine* From the course of these reactions Freund concluded that of the three oxygen atoms in thebaine, of which two are present in methoxy groups, the third belongs to a ring similar to that occurring in diphenylene oxide Hence the complex attached to the phenanthrene nucleus is not $—O\cdot CH_2\cdot CH_2\cdot N\cdot CH_3$ but $—CH_2\cdot CH_2\cdot N\cdot CH_3$ Freund therefore expressed the structure of thebaine by a formula[3] similar to III, p 734, in which however the ethanamine chain is attached to a different position (C 5, see p 733)

Knorr and Pschorr[4] summarise their views on the constitution of the morphine alkaloids in the following statements



1 The three morphine alkaloids are derivatives of 3 6-*dihydroxy-phenanthrylene oxide*

In morphine the hydroxyl groups are present as such, in codeine one of them is methylated, and in thebaine both are methylated

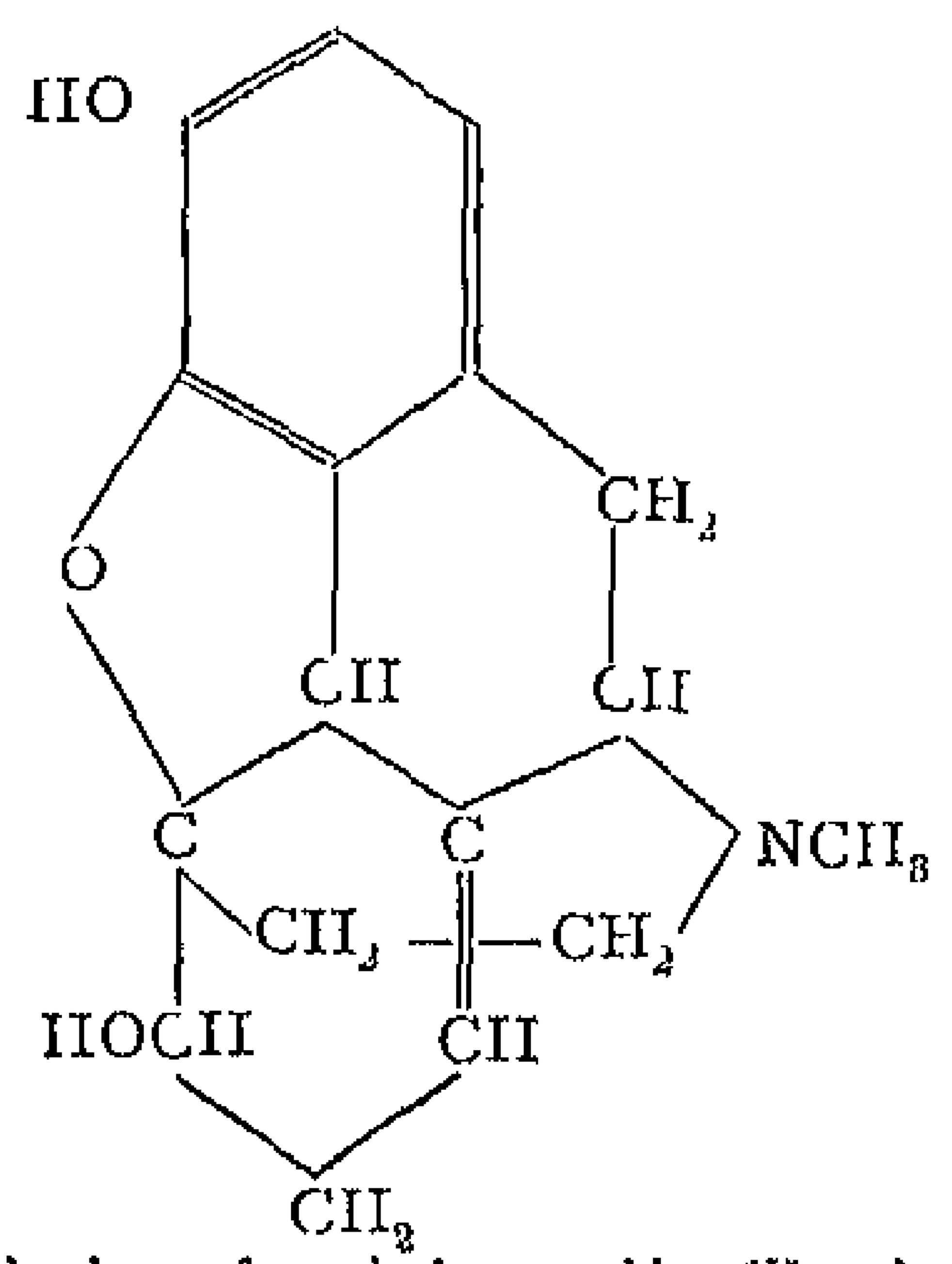
2 Attached to the phenanthrene nucleus as a side ring is the divalent complex $—C_2H_4—N—CH_3$

[1] Thebainone is a ketone obtained by reducing thebaine with stannous chloride and hydrochloric acid (Pschorr, *Ber*, 1905, 38, 3160) It was also isolated by Knorr by the reduction of codeinone (*Ber*, 1905, 38, 3171), hence the ketonic oxygen is in position 6 in the phenanthrene [2] *Ber*, 1905, 38, 3234 [3] M Freund, *Ber*, 1916, 49, 1299 Freund and Speyer, *ib*, 1917, 50, 530 [4] L Knorr and R. Pschorr, *Ber*, 1905, 38, 3176

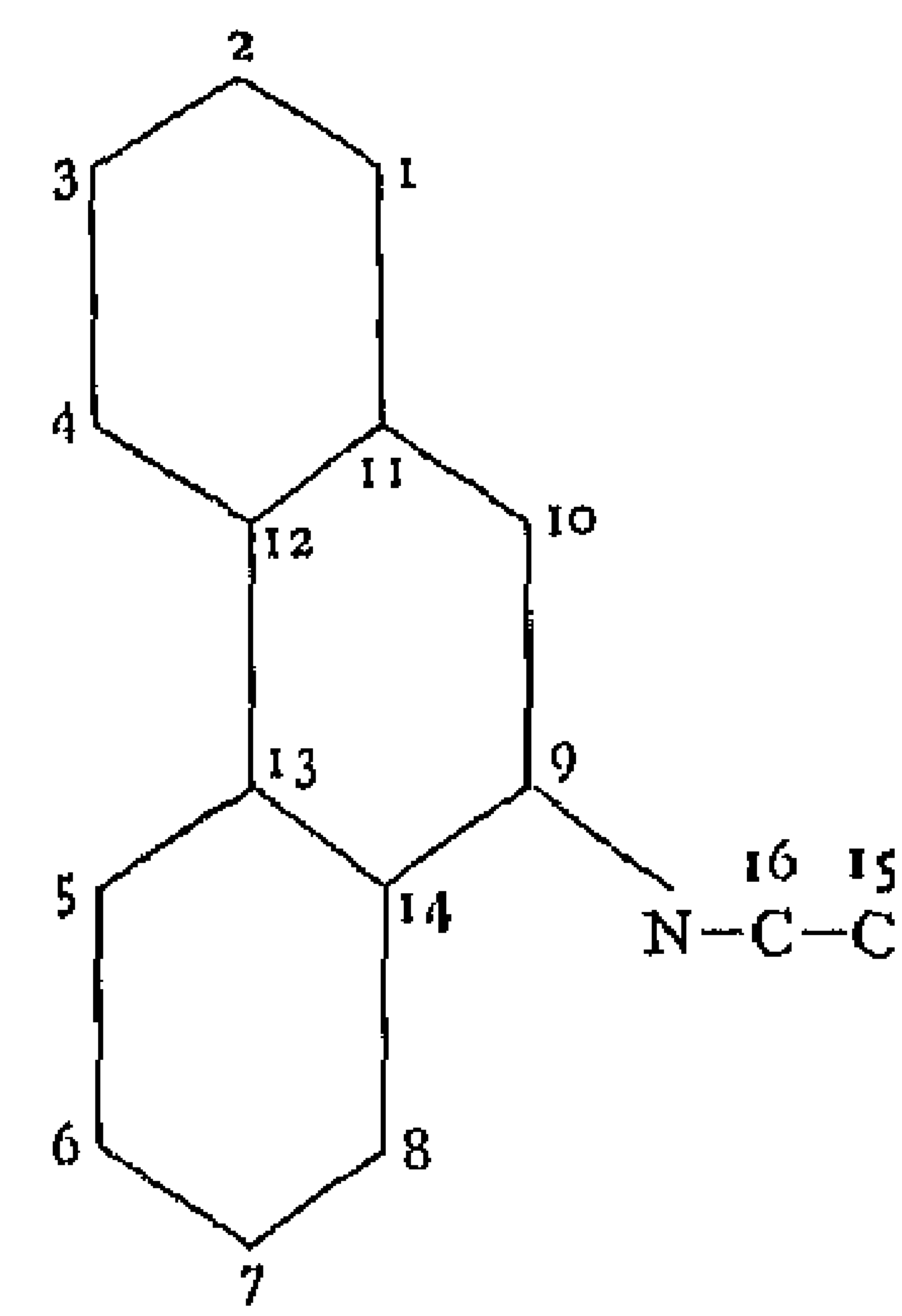
3 The nucleus present in thebaine is tetrahydro-phenanthrene, whilst that in morphine and codeine is hexahydro-phenanthrene The six additional hydrogen atoms in morphine are distributed between rings II and III, whereas ring I, to which the phenolic hydroxyl group is attached, possesses true aromatic properties From the course of the degradation it appears that the complex $-C_2H_4\ N\ CH_3$ belongs to the reduced part of the phenanthrene nucleus

A consideration of all the available facts led Knorr [1] to put forward formula I for morphine in agreement with that advanced by Faltis a year earlier [2]

I



Bridged ring formula for morphine (Knorr)



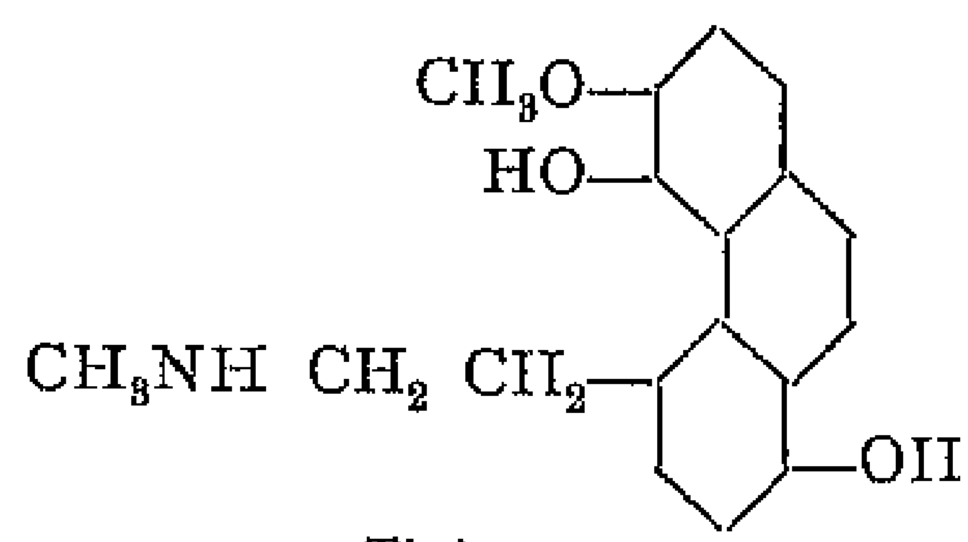
Although these formulæ satisfy most of the experimental facts, there are a number of points which they fail to explain

The points still at issue are the position of the double bond and the mode of attachment of the carbon end of the C—C—N chain to the phenanthrene nucleus In 1925 it was suggested independently by Gulland and Robinson,[3] and by Wieland and Kotake,[4] that the double bond in morphine and codeine should be allocated to position 7 8 instead of 8 14 as in Knorr's formula Further confirmation of this new arrangement is given by the investigation carried out by van Duin, Robinson and Smith [5] on *neopine*, a comparatively rare alkaloid found in opium, which has been shown to be an isomer of codeine having

[1] Knorr, *Ber*, 1907, 40, 3341 [2] Faltis, *J C S*, 1906, A, i, 979 Direct experimental evidence for the existence of a double bond in codeine is provided by oxidation of the latter to the glycol, dihydroxy-dihydrocodeine, on treatment with dilute aqueous permanganate (R S Cahn and R Robinson, *J C S*, 1926, 908) [3] J M Gulland and R Robinson, *Manchester Lit and Phil Soc*, 1925, No 10 Nature, 1925, 115, 625 [4] Wieland and Kotake, *Ann*, 1925, 444, 69, *Ber*, 1925, 58, 2009 [5] van Duin, Robinson and Smith, *J C S*, 1926, 903

the double bond in the 8 14-position Certain other workers[1] have now adopted the Δ-7 8 structure for morphine and codeine

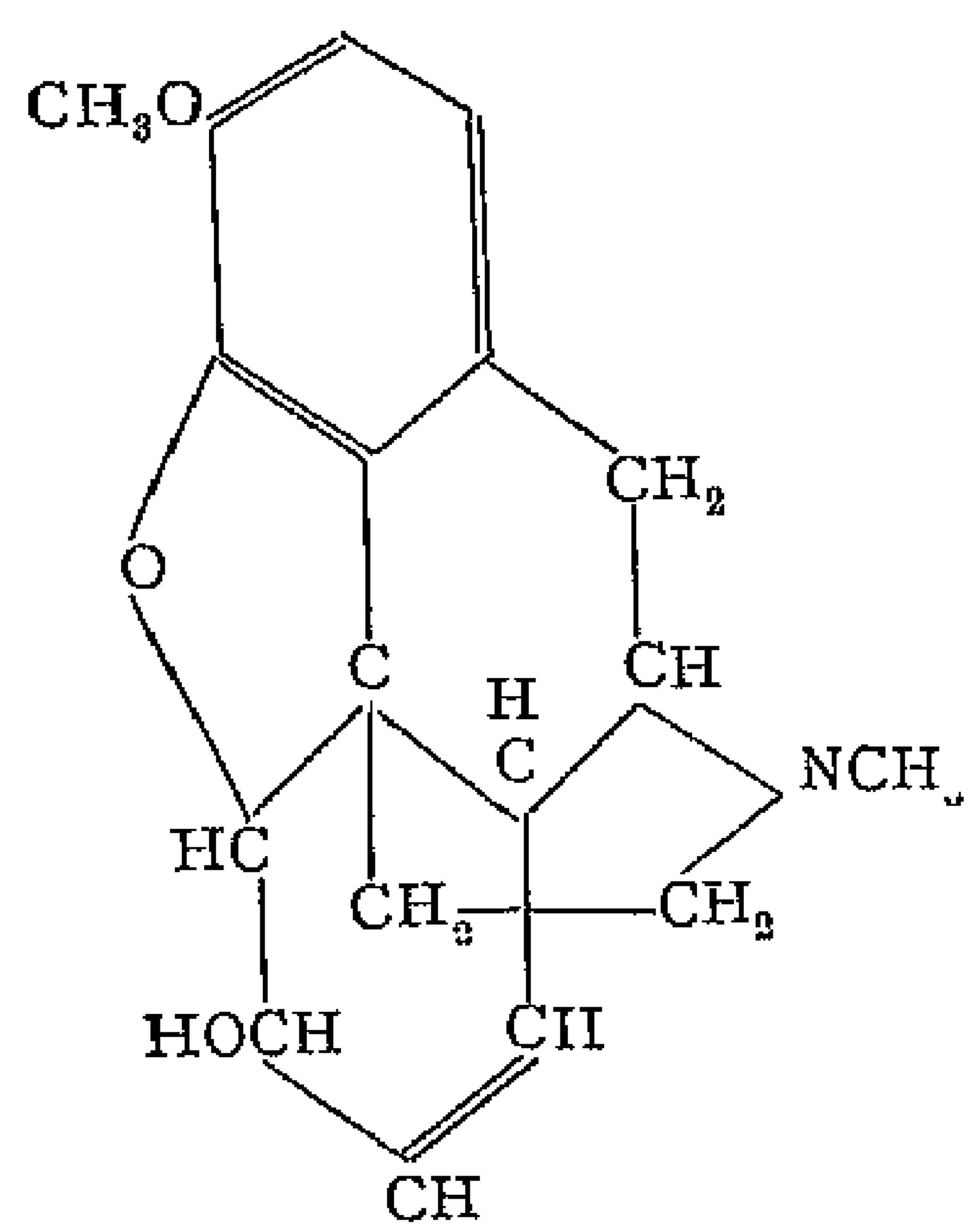
In 1923 Gulland and Robinson[2] advanced arguments in favour of a C 13 or C 14 linkage for the ethanamine side chain, a modification which is supported indirectly by Schopf's proof[3] that the union is not in the C 5 position, and also by the direct experimental work of Wieland and Small[4] and Gulland[5] The final choice between C 13 and C 14 is complicated by the surprising migrations which may occur in the alkaloids of this group under relatively mild experimental conditions, leading to the formation of derivatives containing substituents at C 5, C 13 or C 14 For example thebaine on being heated for a short time with dilute hydrochloric acid yields *thebenine*, in which the C—C—N chain is found attached to the 5-position[6] On the whole, however, the evidence indicates C 13 as the most probable point of attachment, as in formula II



Thebenine

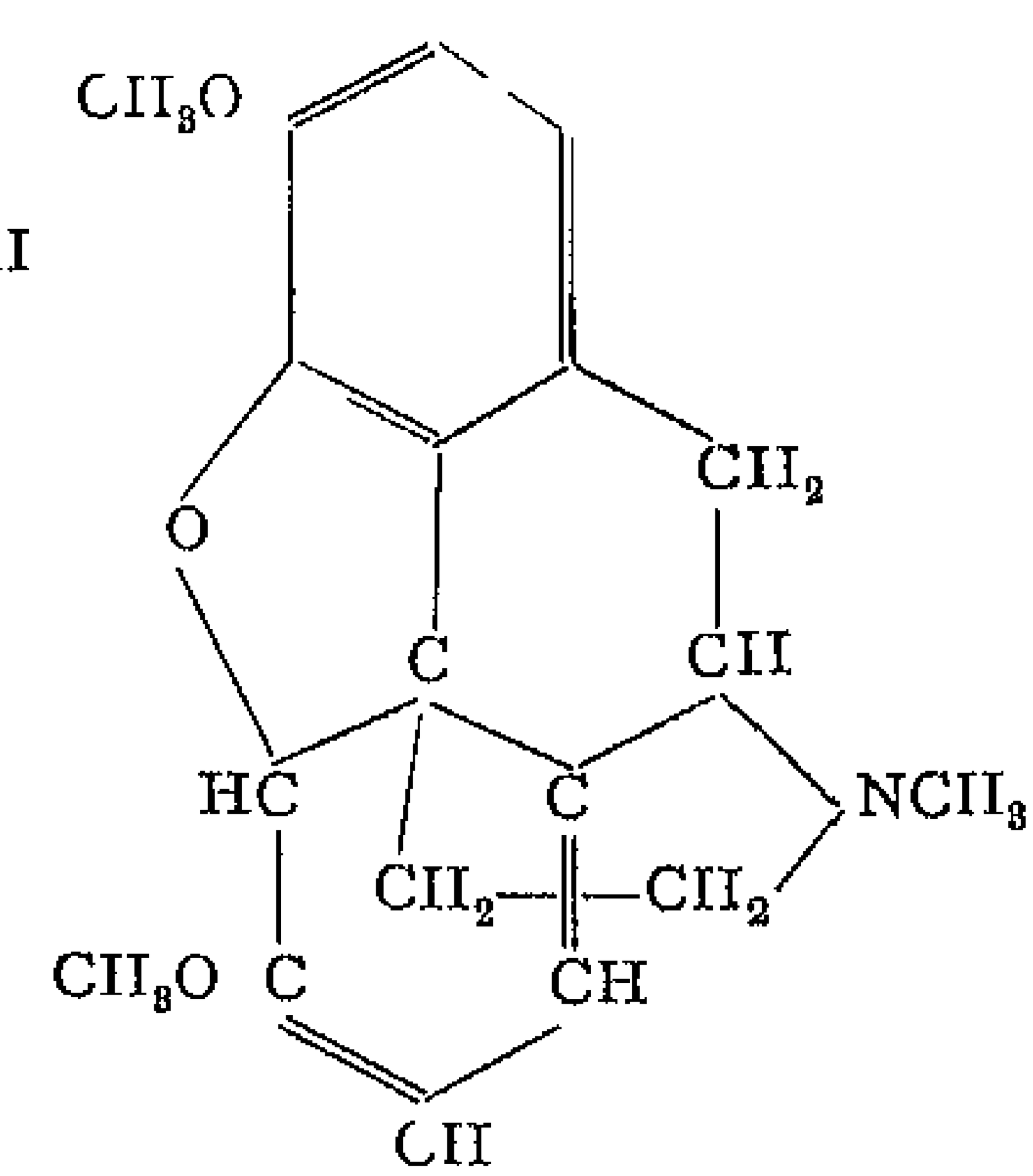
Thebaine is a less hydrogenated alkaloid represented by Gulland and Robinson as having formula III, identical with that of Knorr

II



Codeine
(Gulland and Robinson)

III



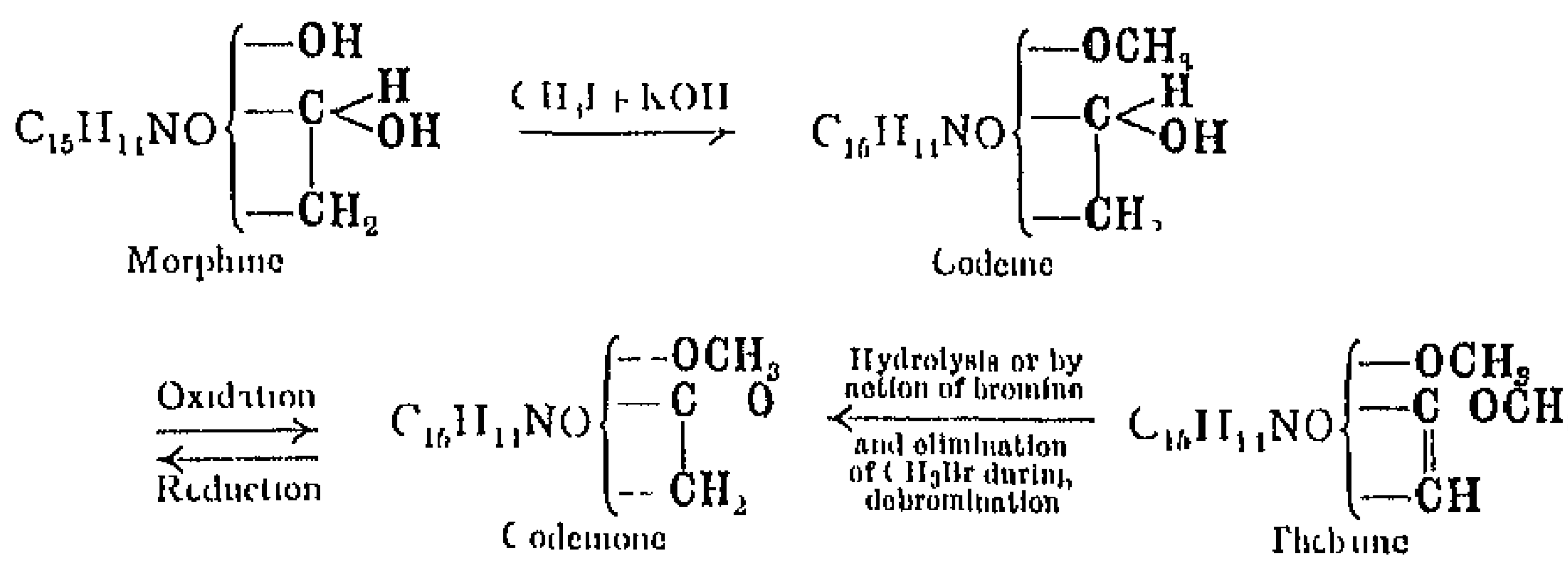
Thebaine
(Gulland and Robinson)

[1] J v Braun and R S Cahn, *Ann*, 1926, 451, 55 C Schopf, *Ann*, 1927, 452, 211 [2] Gulland and Robinson, *J C S*, 1923, 980, 998 [3] Schopf, *loc cit* [4] Wieland and Small, *Ann*, 1928, 467, 17 [5] J M Gulland, *J C S*, 1928, 702 [6] Knorr, *Ber*, 1903, 36, 3074 Pschorr, *ibid*, 1904, 37, 2780, 1907, 40, 2001, *Ann*, 1910, 373, 51, 77 J M Gulland and C J Virden, *J C S*, 1928, 921

except for the different point of union of the C—C—N chain. The formula is supported by Schöpf's reduction of thebaine to tetrahydrothebane.[1]

Conversion of Thebaine into Codeine

As has already been explained, thebaine resembles morphine and codeine in constitution, but represents a different degree of hydrogenation of the phenanthrene nucleus. Attempts were therefore made to establish an experimental connection between these two structures. This was successfully accomplished by Knorr[2] through the compound codeinone, obtained by oxidising codeine with chromic acid or potassium permanganate.[3] The changes involved are summarised in the following scheme, in which the heavy type denotes groups taking part in the reactions:



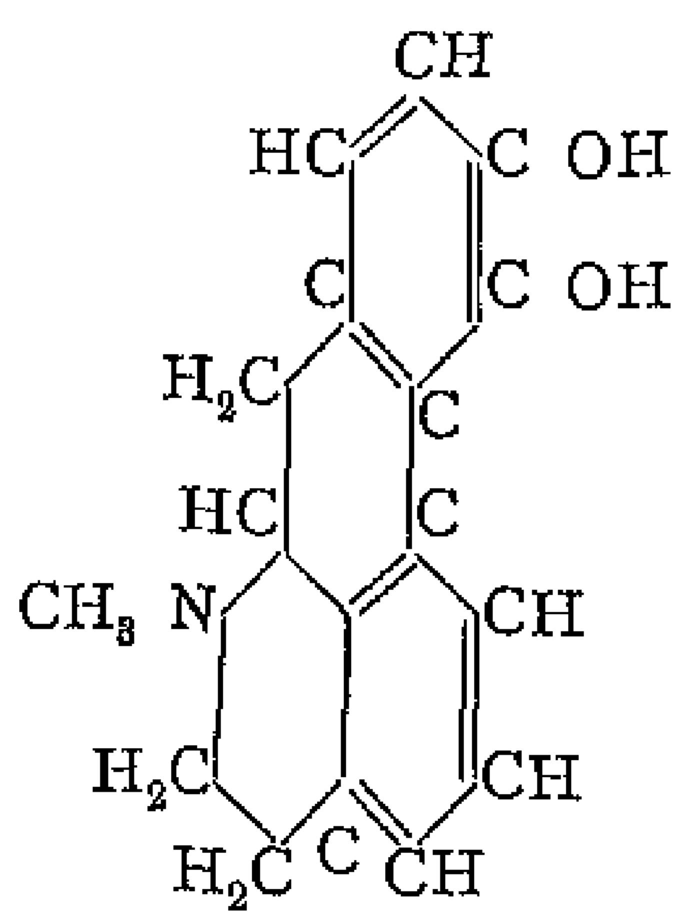
As is apparent from the above formulæ, codeinone is the ketone corresponding to the alcohol codeine. It is also closely related to thebaine, which according to Knorr (*loc cit*) is the *methyl ether of the enolic form of codeinone*. In this respect thebaine is related to codeinone in the same way as codeine is to morphine. It was therefore of interest to discover a means of converting thebaine into codeinone and codeinone into thebaine.

The first part of the problem has already been solved in two ways, as indicated above. On the one hand, Knorr succeeded in converting thebaine into codeinone by simple hydrolysis with hot or cold dilute acids, and on the other, Freund observed the formation of codeinone from the bromo-derivative of thebaine.

Eukodal[4] is the hydrochloride of dihydro-hydroxy-codeinone, $C_{18}H_{21}O_4N, HCl$. It is a white powder which melts unsharply at 270°. Like codeine and morphine it is a narcotic, but is more rapid in its action than either of these. It exerts no harmful influence on the heart.

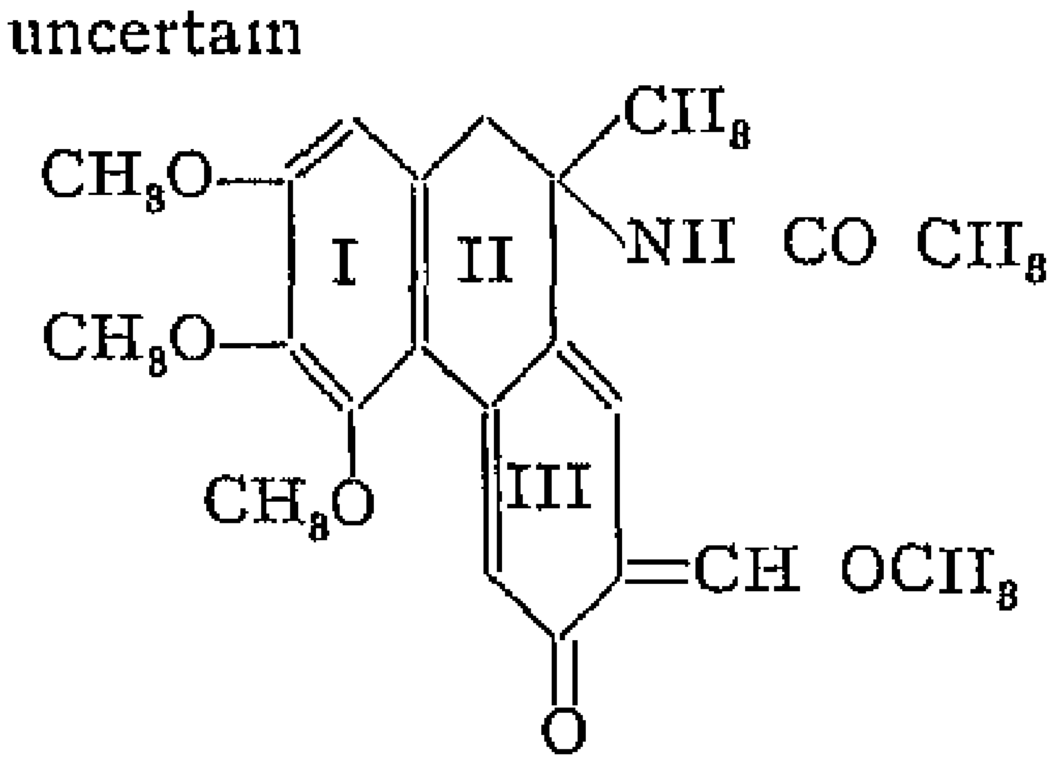
[1] Schöpf, *loc cit*. [2] L Knorr, *Ber*, 1906, 39, 1409; Freund, *Ber*, 1906, 39, 844. [3] Ach and Knorr, *Ber*, 1903, 36, 3067. [4] M Freund and F Speyer, *Münch med Wochenschr*, 1927, 380; E Merck's *Jahresbericht*, 1916, 307.

Apomorphine, which has been mentioned on p 727, is obtained by the action of dehydrating agents on morphine Physiologically, it has quite different properties from morphine, it is no longer a narcotic, but is an expectorant and emetic Pschorr[1] has shown that its composition corresponds in all probability to the annexed formula This structure has recently been confirmed by the synthesis of *dl*-apomorphine dimethyl ether[2] Apomorphine methobromide is also used therapeutically as an emetic under the name *euporphine*[3] The latter is less violent in its action than apomorphine, consequently it produces less strain on the heart and may be used for a longer period without danger to the patient



ALKALOIDS OF THE MEADOW SAFFRON

To this group belong colchiceine, $C_{21}H_{23}NO_6+\frac{1}{2}H_2O$, and colchicine, $C_{22}H_{25}NO_6$ **Colchicine** melts at 143° to 147° and is very poisonous It is employed medicinally in cases of rheumatism and gout A Windaus[4] has shown that the alkaloid is derived from 9 methyl-phenanthrene, and assigns it the following structure in which the position of substituents in ring III is still uncertain



Colchicine

VIII

Azines

Under the heading of *azines* are grouped various classes of compounds containing a six-membered ring built up of carbon and two or more atoms of nitrogen, or of carbon and nitrogen together

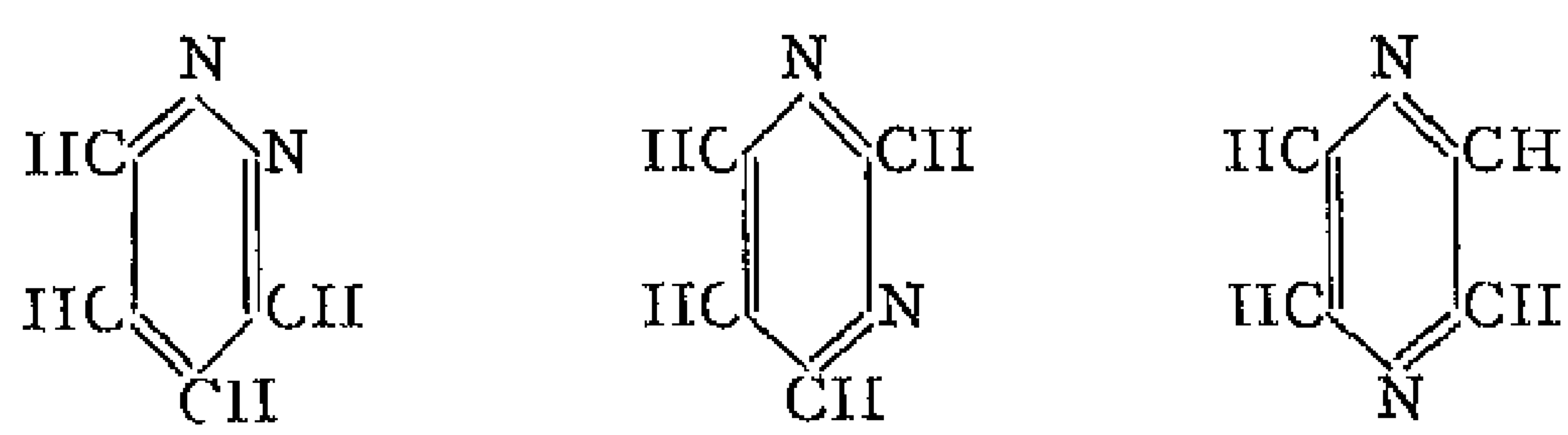
[1] Pschorr and collaborators, *Ber*, 1902, 35, 4377, 1907, 40, 1980 [2] Avenarius and Pschorr, *Ber*, 1929, 62, 321 E Spath and O Hromatka, *ibid*, p 325 See, however, Gulland and co-workers, *J C S*, 1929, 1791, 1666 [3] *C*, 1905, I, 702, 1906, I, 1067 [4] A Windaus, *Ann*, 1924, 439, 59

with oxygen or sulphur Compounds of this type containing oxygen are termed *oxazines*, those containing sulphur are known as *thiazines*

The azines are usually named in accordance with the number of nitrogen atoms in the ring, *e.g.* diazines, triazines, tetrazines, etc These six-membered rings may be compared with the five-membered azole rings previously described Belonging to this group are important classes of dye stuffs

I — DIAZINES

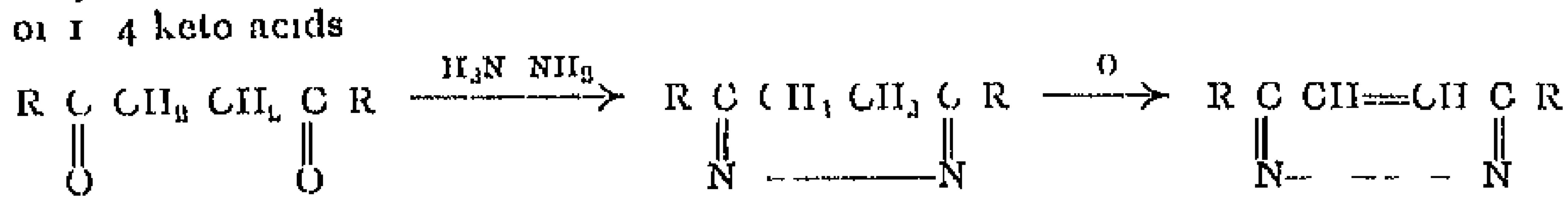
The simplest azines, containing a ring composed of four carbon atoms and two nitrogen atoms, will be taken first Three series of diazines are theoretically possible, derived from the following compounds —



Orthodiazine, Pyridazine — Metadiazine, Pyrimidine — Paradiazine, Pyrazine

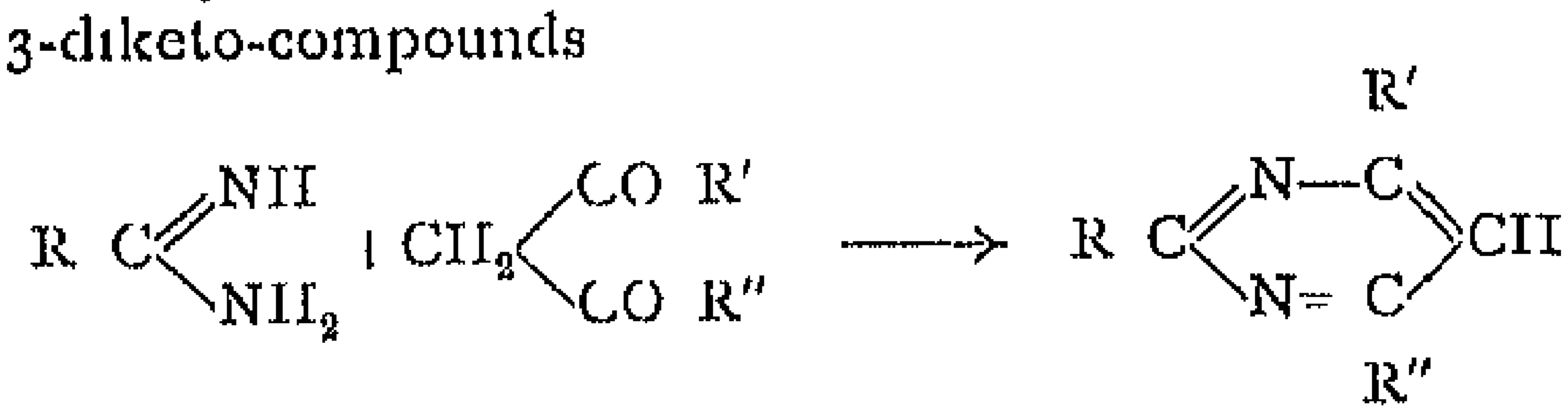
All of these are known

Orthodiazines or **pyridazines** can often be prepared by the oxidation of their dihydro derivatives, obtained by the condensation of hydrazines with 1 4 diketones or 1 4 keto acids



The parent substance, *pyridazine*, results from the action of hydrazine hydrate on the acetin of nitro succinaldehyde, O CH CH(NO_2) CH CH O CO CH_3, fumaraldehyde being formed as an intermediate compound[1] It is a colourless liquid, b p 205° at 755 5 mm The base has an odour resembling that of pyridine, and the majority of its salts are readily soluble in water

Metadiazines or **pyrimidines**, which include the cyclic ureides and purines, play an important part in physiological processes They may be prepared by condensing the amidines of various carboxylic acids with 1 3-diketo-compounds

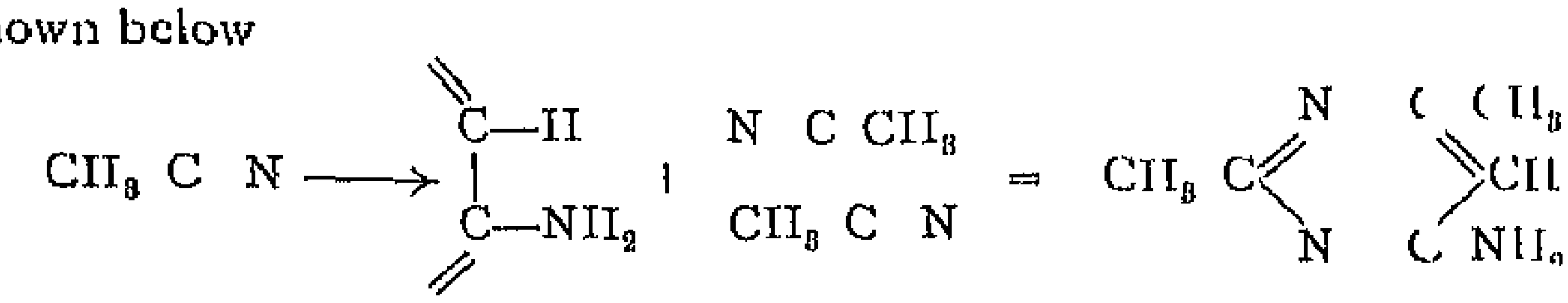


Amidines, urea and urea derivatives condense with cyano-acetic acid to give substituted pyrimidines containing an amino-group in

[1] R Marquis, *J C S*, 1903, A, 1, 370 See also E Täuber, *Ber*, 1895, 28, 451 S Gabriel, *Ber*, 1909, 42, 654 M Lange, *Ber*, 1909, 42, 576

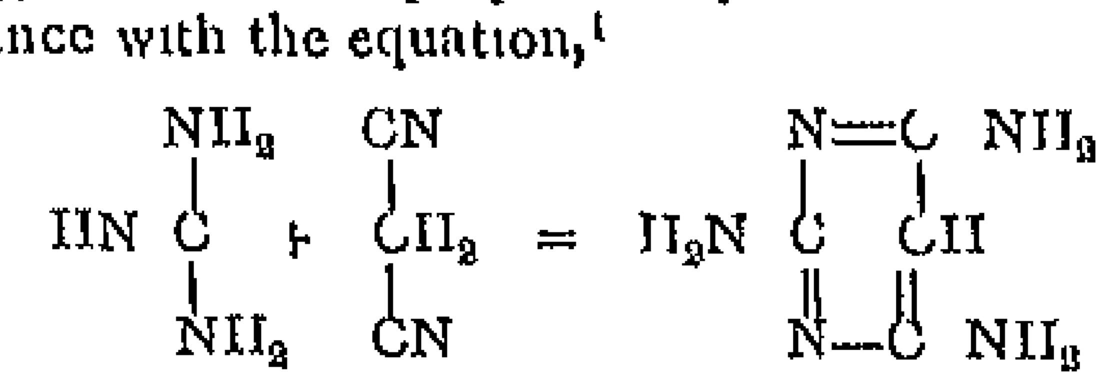
position 4 These compounds are used in the synthesis of various xanthine bases[1] (see p 342)

Pyrimidine derivatives are also obtained by the condensation of dicyandiamide, or of guanyl urea, with malonic ester, acetoacetic ester, cyano-acetic ester or their derivatives[2] The polymerisation products of aliphatic nitriles known as **cyanalkines**,[3] which have been mentioned in an earlier chapter, are also amino-pyrimidines These are formed under the influence of sodium It is assumed that two hydrogen atoms in a molecule of nitrile migrate from carbon to nitrogen, and that the resulting complex then unites with two other molecules of nitrile, as shown below



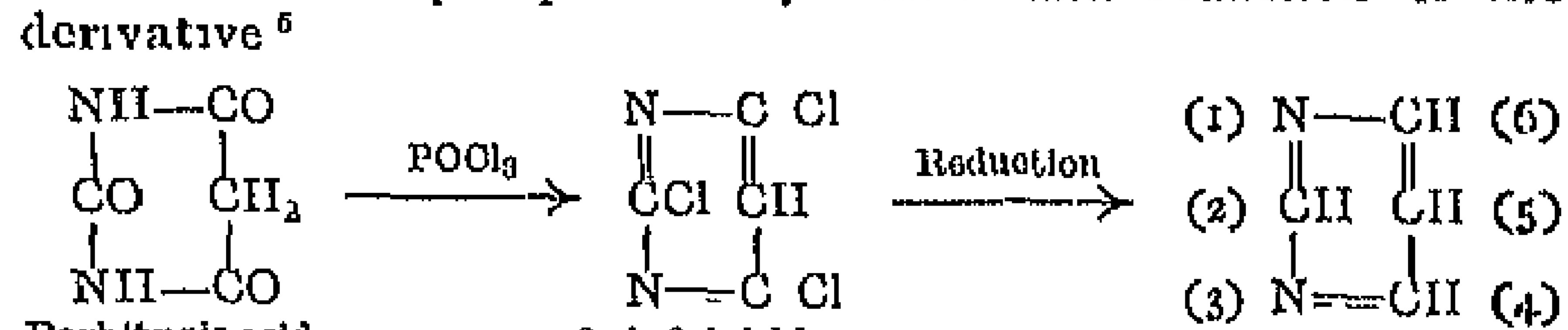
Labile hydrogen is therefore necessary for the formation of a cyanalkine Hence only primary nitriles (RCH_2CN), which contain two hydrogen atoms attached to the α-carbon atom, can undergo such a change A mixture of nitriles will react together in this way if at least one of them is of primary character Tertiary nitriles give compounds of the cyanuric series This change is brought about even more readily by use of sodamide It is also possible to use sodium methoxide, the reaction being carried out in sealed tubes at a temperature of 130° to 140°

2 4 6 *Triamino pyrimidine* is prepared by the action of malono nitrile on guanidine, in accordance with the equation,[4]



Whereas the pyrimidines are strongly basic in character, the oxypyrimidines possess both basic and phenolic properties

Pyrimidine, the parent compound of this group, is best prepared from barbituric acid, by treatment with phosphorus oxychloride and reduction of the resulting trichloro derivative[5]

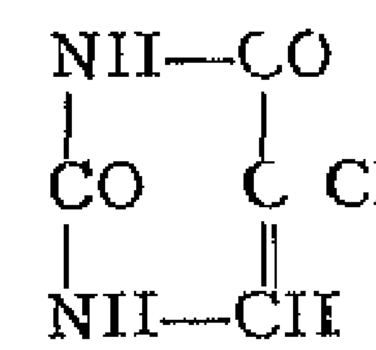


Barbituric acid — 2 4 6 Trichloro pyrimidine — Pyrimidine

It is a crystalline compound of narcotic odour, and dissolves readily in water It melts at 21° and boils at 124°

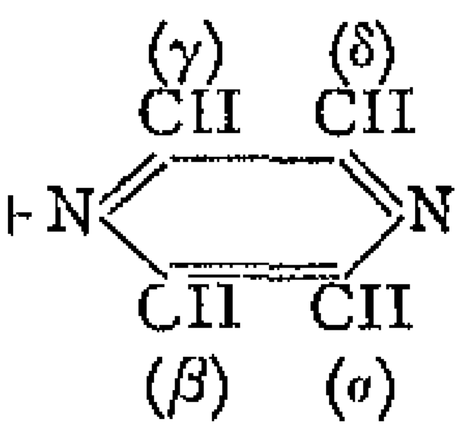
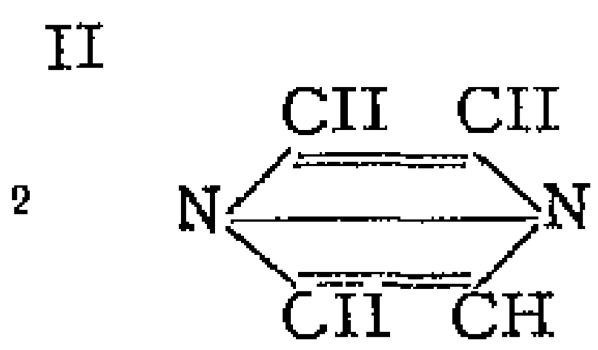
[1] W Traube, *Ber*, 1900, 33, 1371, 3035, 1904, 37, 2267 [2] *J C S*, 1906, A, i, 705 [3] For further details, see E v Meyer, *J C S*, 1906, A, i, 411 [4] Traube *Ber*, 1904, 37, 4544 [5] Gabriel, *Ber*, 1900, 33, 3666

Deıivatıves of pyımıdıne are of great ımportance physıologıcally, l take paıt ın a numbeı of fundamental lıfe processes For ample, they have been shown by Kossel to be present the cell nucleus, wheıe the synthetıc changes ›ocıated wıth the growth of the cell take place A ıple pyıımıdıne deıivatıve ıs *thymıne*,[1] oı 5-methyl-6-dıhydroxy-pyrımıdıne, whıch can be obtaıned ın ge quantıties fıom anımal and vegetable nucleıns e p 770) It has also been synthesised by E Fıscheı



Thymine

The **paradiazines** oı **pyrazines** aıe prepared by the elımınatıon of teı and hydıogen from α-amıno-aldehydes oı α-amıno-ketones, *e g*,

$_2N$ CH_2 CHO = $2H_2O + H_2 +$  or[2] 

As a ıesult of thıs method of pıepaıatıon, these compounds aıe also lled **aldines** or **ketines** They aıe weak bases, theır salts beıng dıolysed ın aqueous solutıon When ıeduced wıth sodıum and ohol, pyrazınes aıe converted ınto the hexahydro-deıivatıves oı **perazines**, whıch are analogous to the pıpeııdınes

Pyrazine ıtself ıs produced by the condensatıon of amıno-etaldehyde oı amıno-acetal It melts at 55°, boıls at 115°, and has ı odour of helıotrope Its ıeductıon product, *pıperazıne*, whıch a stıong dıacıd base, has alıeady been descııbed on p 240

γ-*Dımethyl-pyıazıne*, *ketıne*, $C_4H_2(CH_3)_2N_2$, ıs a lıquıd boılıng at 153° ıs obtaıned fıom ısonıtıoso-acetone by ıeductıon, amıno-acetone beıng ımed as an ınteımedıate pıoduct It may also be pıepared by the stıllatıon of glyceıol wıth ammonıum salts The taıtıate of $\alpha\gamma$-methyl-pıpeıazıne (obtaıned by reducıng $\alpha\gamma$-dımethyl pyıazıne) has en used, undeı the name of **lycetol**, as a solvent for uııc acıd ın cases gout Pıpeıazıne has also been employed foı the same puıpose

Among other deıivatıves of pıpeıazıne aıe the 2 5-*dıketo-perazınes*, descııbed on p 215 These have been used ın the nthesıs of polypeptıdes Dıalkyl-dıketo-pıperazınes have also been nthesısed[3]

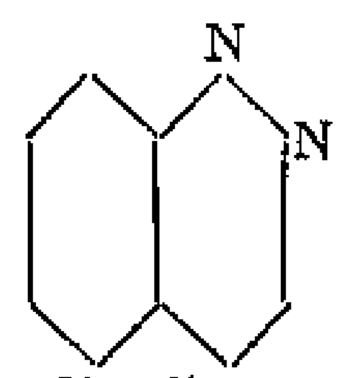
II —BENZO-DIAZINES

The ııng systems descrıbed under dıazınes may also occur ın ombınatıon wıth benzene nucleı, thus gıvıng ııse to a numbeı of new asses of compounds These aıe teımed mono-benzo-dıazınes oı

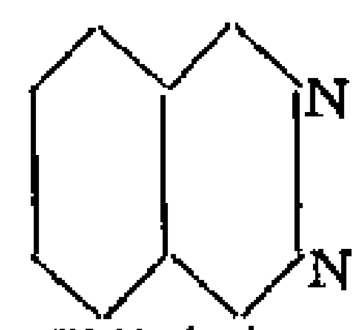
[1] For the detectıon of thymıne, see T B Johnson and Baudısch, *J Am C S*, 1921, **43**, 2670
It has not yet been possıble to decıde between formulæ I and II for pyrazıne, but the former ıll be used ın the succeedıng pages For evıdence supportıng foımula II, see L Wolff, *Beı*, 393, **26**, 722 [3] Rosenmund, *Beı*, 1909, **42**, 4470

dibenzo diazines, according as one or two benzene nuclei are condensed with the diazine ring

From pyridazine are derived *cinnolines*[1] and *phthalazines*



Cinnoline

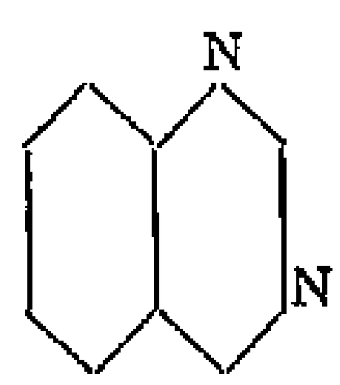


Phthalazine

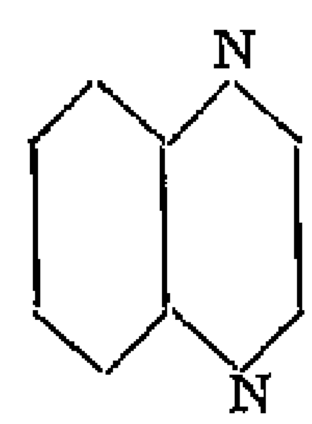
Phthalazine is obtained by the action of hydrazine on ortho derivatives of benzene which are brominated in the side chain[2]

$$C_6H_4\left\langle\begin{array}{l}CHBr_2\\ CHBr_2\end{array}\right. + \begin{array}{l}H_2N\\ \ \ |\\ H_2N\end{array} = C_6H_4\left\langle\begin{array}{l}CH\ N\\ \quad\ \ |\\ CH\ N\end{array}\right. + 4HBr$$

Pyrimidines and pyrazines give rise respectively to quinazolines and quinoxalines



Quinazoline



Quinoxaline

Quinazolines are prepared by the action of ammonia on acyl derivatives of *o* amino benzaldehydes

$$C_6H_4\left\langle\begin{array}{l}NH\ CO\ CH_3\\ CHO\end{array}\right. + NH_3 = C_6H_4\left\langle\begin{array}{l}N : C\ CH_3\\ \quad\ \ \ |\\ CH\ N\end{array}\right. + 2H_2O$$

They are strong bases, which are readily reduced to their dihydro compounds *Quinazoline* itself is a solid, m p 48° and b p 243° It is obtained from *o* nitro-benzylamine (I), which is first reduced to *o* amino benzylamine (II) The latter is then treated with formic acid, and the dihydro quinazoline (III) so obtained is oxidised to quinazoline[3] (IV)

$$\text{I}\quad C_6H_4\left\langle\begin{array}{l}NO_2\\ CH_2\ NH_2\end{array}\right. \longrightarrow \quad \text{II}\quad C_6H_4\left\langle\begin{array}{l}NH_2\\ CH_2\ NH_2\end{array}\right. \longrightarrow$$

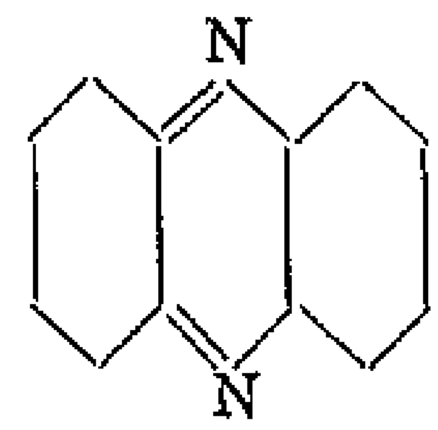
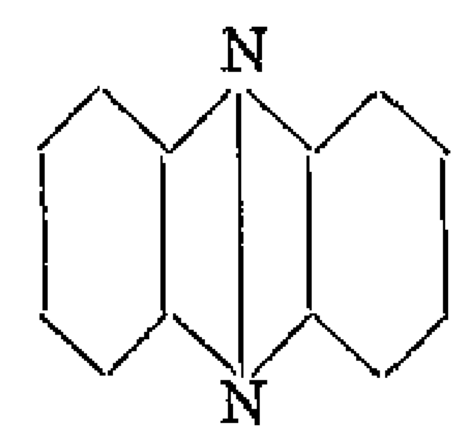
$$\text{III}\quad C_6H_4\left\langle\begin{array}{l}N{=}CH\\ \quad\ \ |\\ CH_2\ NH\end{array}\right. \longrightarrow \quad \text{IV}\quad C_6H_4\left\langle\begin{array}{l}N{=}CH\\ \quad\ \ |\\ CH : N\end{array}\right.$$

The preparation of **quinoxalines** by the condensation of *o* diamines with 1 2 diketones has been mentioned on pp 249 and 387 These are weakly basic compounds, which may be reduced to hydro quinoxalines, but are stable towards oxidising agents

In the dibenzo-diazine series the most interesting compounds are the **dibenzo paradiazines** or **phenazines** Several important classes of dye-stuffs, such as the eurhodines, indulines and safranines, belong to this group

[1] See also Busch and Rast, *Ber*, 1897, **30**, 521 R Stoermer and H Fincke, *Ber*, 1909, **42**, 3115 O Widmann, *ibid*, 4216 [2] For other methods, see S Gabriel, *Ber*, 1903, **36**, 3373 [3] Gabriel and Colman, *Ber*, 1904, **37**, 3643

The simplest example is *phenazine*, which may be represented by either of the formulæ I or II below. Formula I, containing two quinonoid linkings, will be used in the following pages.

I  II 

Phenazine crystallises in bright yellow needles, m.p. 171°, and is easily sublimed. It may be prepared in several ways, *e.g.* by heating nitrobenzene with aniline[1] at 140°, in the presence of sodium hydroxide. This reaction is probably to be represented as follows:

$$C_6H_5 \cdot NO_2 \longrightarrow C_6H_4\begin{cases}(1)\ OH\\(2)\ NO\end{cases} \xrightarrow[-H_2O]{+C_6H_5 \cdot NH_2}$$

$$C_6H_4\begin{cases}NH\\N(OH)\end{cases}C_6H_4 \xrightarrow{-H_2O} C_6H_4\begin{cases}N\\|\\N\end{cases}C_6H_4$$

Phenazine may also be synthesised by heating a mixture of catechol and *o*-phenylene diamine. In general, phenazines are formed by the action of *o*-diamines on *o*-quinones:

$$R\begin{cases}O\\O\end{cases} + \begin{cases}H_2N\\H_2N\end{cases}R = R\begin{cases}N\\N\end{cases}R + 2H_2O$$

The majority of the phenazines are yellow, weakly basic compounds, which distil unchanged. Their colour is due to the presence of the chromophore group $\begin{cases}N\\N\end{cases}$. Simple azines, such as phenazine, tolu-phenazine, $CH_3 \cdot C_6H_3N_2C_6H_4$, naphtho-phenazine,[2] $C_{10}H_6N_2C_6H_4$, naphthazine, $C_{10}H_6N_2C_{10}H_6$, phenanthra-phenazine, $C_{14}H_8N_2C_6H_4$, and anthrazine, $C_{14}H_8N_2C_{14}H_8$, are not in themselves dye stuffs. But they become so on the entrance of amino or hydroxyl groups into the molecule. Before proceeding further, it should be mentioned that, in addition to the usual formulæ of types I and II for the amino- and hydroxy-phenazines, the para-quinonoid formulæ I*a* and II*a* have certain advantages, although the basic properties of the amino-compounds and the phenolic properties of the hydroxyl compounds support I and II.

[1] Wohl and Aue, *Ber.*, 1901, 34, 2442.

[2] αβ Naphtho-phenazine is obtained by the condensation of α nitroso β naphthol with *o* phenylene diamine. F. Ullmann and R. Heisler, *Ber.*, 1909, 42, 4263.

Amino phenazine	I	$C_6H_4\langle{}^{N}_{N}\rangle C_6H_3\ NH_2$
or	I*a*	$C_6H_4\langle{}^{N}_{NH}\rangle C_6H_3{=}NH$
Hydroxy phenazine	II	$C_6H_4\langle{}^{N}_{N}\rangle C_6H_3\ OH$
or	II*a*	$C_6H_4\langle{}^{N}_{NH}\rangle C_6H_3{=}O$

Careful consideration of all the facts has led to the conclusion that these compounds are probably tautomeric, each reacting in the two forms indicated A few of the more important dyes belonging to this series are described in the following pages.

1 Eurhodines or Aminophenazines[1]

The eurhodines may be prepared by the following general methods

1 By the condensation of quinones with triamines containing two amino groups in the ortho-position to one another, or by the condensation of amino-quinones with ortho-diamines (Compare phenazine, p 741)

2 By the action of nitroso-dimethylaniline, or of quinone dichlorodi-imines (see p 424), on certain monamines which are substituted in the para-position

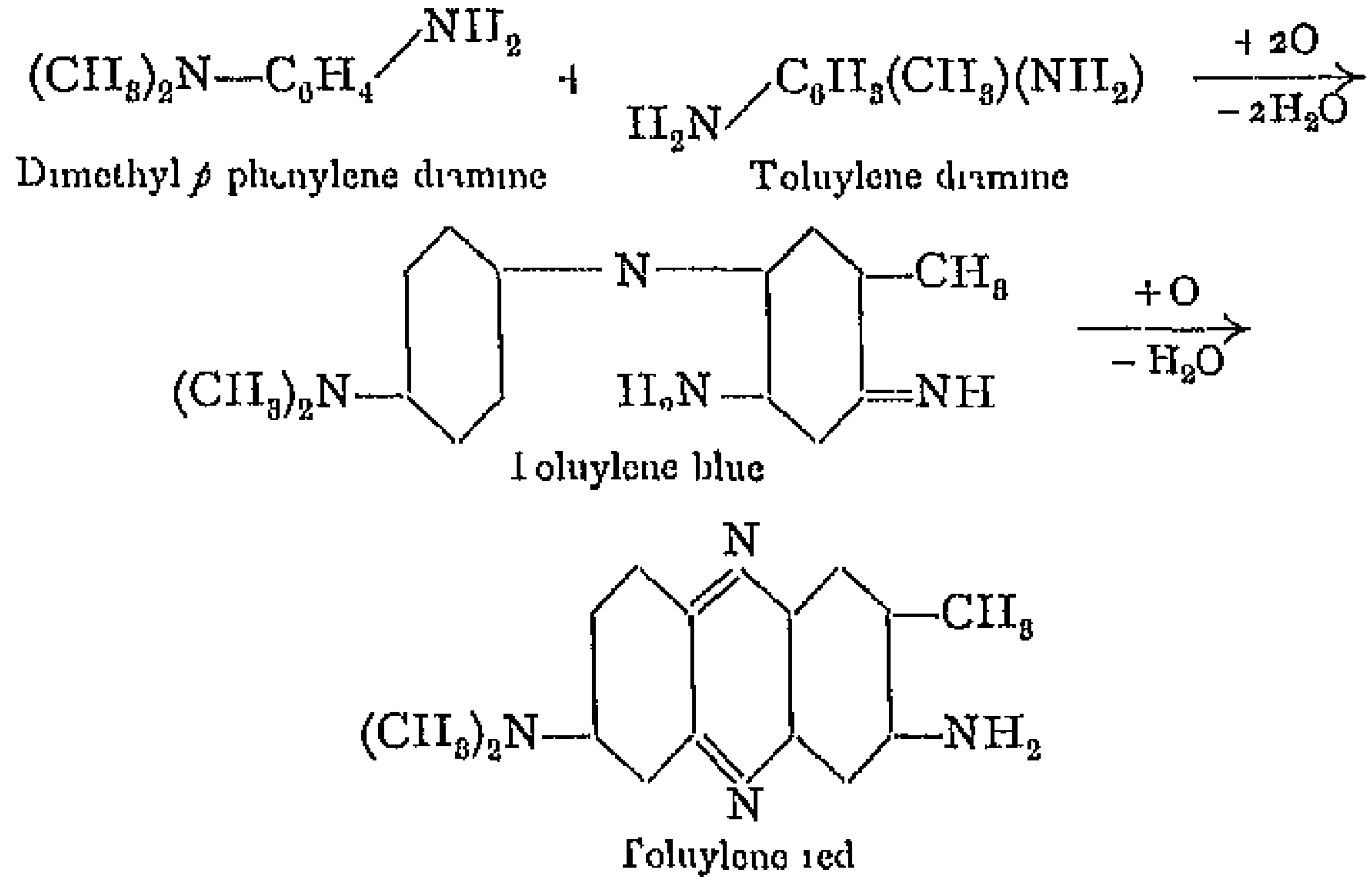
3. By the action of *o*-aminoazo-compounds on monamines It was in this way that Witt obtained the first eurhodine, by heating *o*-amino-azo-*p*-toluene with *a*-naphthylamine

$$\underset{o\text{ Amino-azotoluene}}{C_7H_6\langle{}^{N\ NC_7H_7}_{NH_2}} + \underset{\alpha\text{-Naphthylamine}}{C_{10}H_7NH_2} \longrightarrow C_7H_6N_2C_{10}H_5NH_2$$

The simplest eurhodines are weakly basic dye-stuffs, giving monacid salts which dye silk a red colour As, however, the salts are dissociated in water, this red colour is changed into the yellow of the base on washing

Toluylene red is formed by oxidising a mixture of dimethyl-*p* phenylene diamine and *m*-toluylene diamine at the boiling-point *Toluylene blue*, an indamine derivative, occurs as an intermediate product and is converted into toluylene red by elimination of hydrogen

[1] O Witt, the discoverer of the eurhodines, only applied this name to the monamino-azines. At the present time the term is used generally, to include all amino azines



Toluylene red crystallises in orange-red needles, dyes silk and tannin-mordanted cotton a scarlet red, and is used commercially under the name of "neutral red"

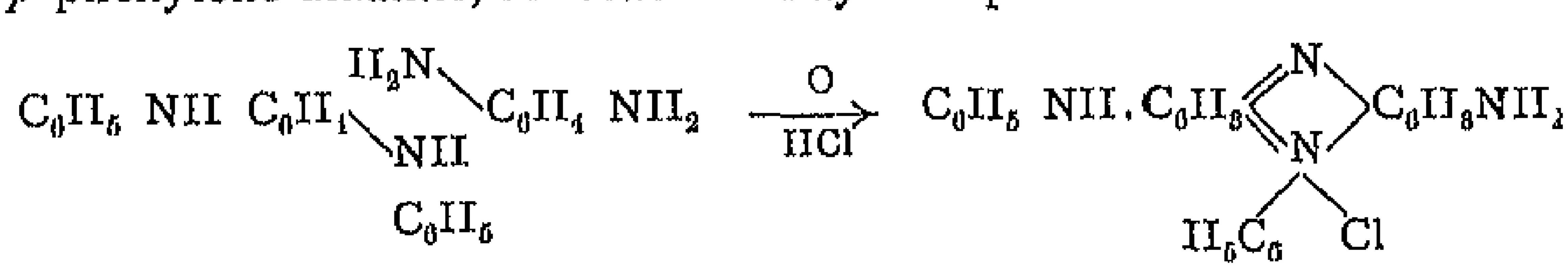
2 Eurhodols, or Hydroxyphenazines

These are obtained by the action of concentrated hydrochloric acid on eurhodines at 180°, and also by the fusion of phenazine sulphonic acids with potassium hydroxide. In their dyeing properties they resemble the eurhodines, but differ in having both basic and phenolic properties

3 Safranines, Aposafranines and Indulines

The safranines are diamino-azines containing at least three hydrocarbon nuclei. They are strongly basic crystalline compounds, which are readily soluble in water and dye yellowish red to violet colours. They may be prepared by the following reactions —

1 By the oxidation of a mixture of a m-amino-diphenylamine and a p-diamine. In the case of diphenyl-m-phenylene diamine and p-phenylene diamine, the reaction may be represented as follows —

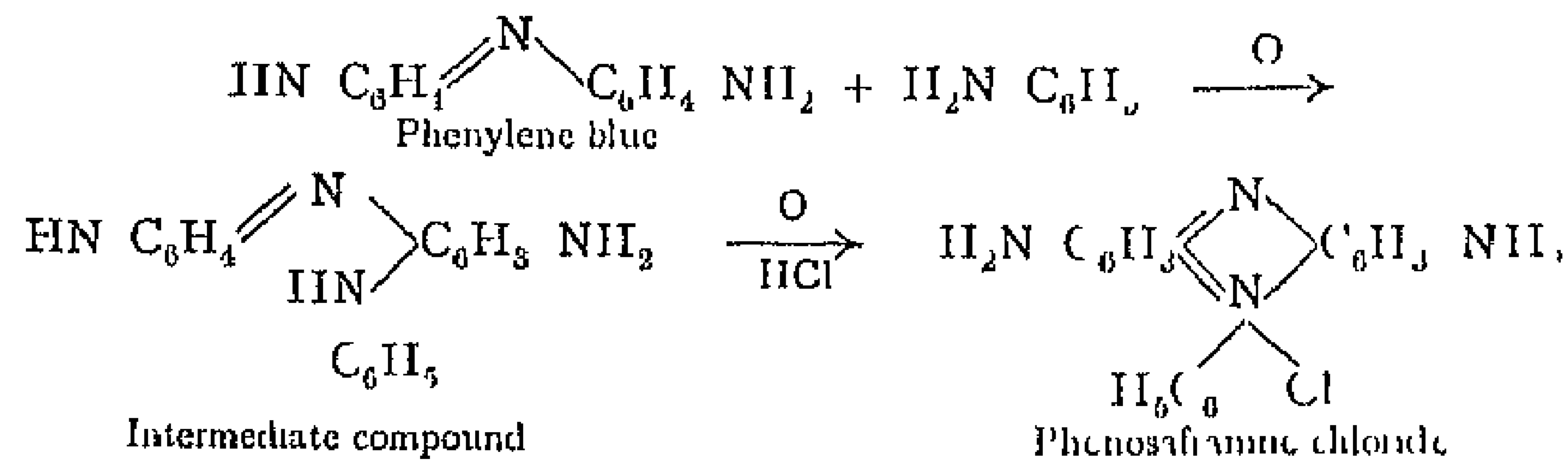


2 By the oxidation of a mixture of a p-diamino-diphenylamine, or of an indamine, with a primary monamine [1]

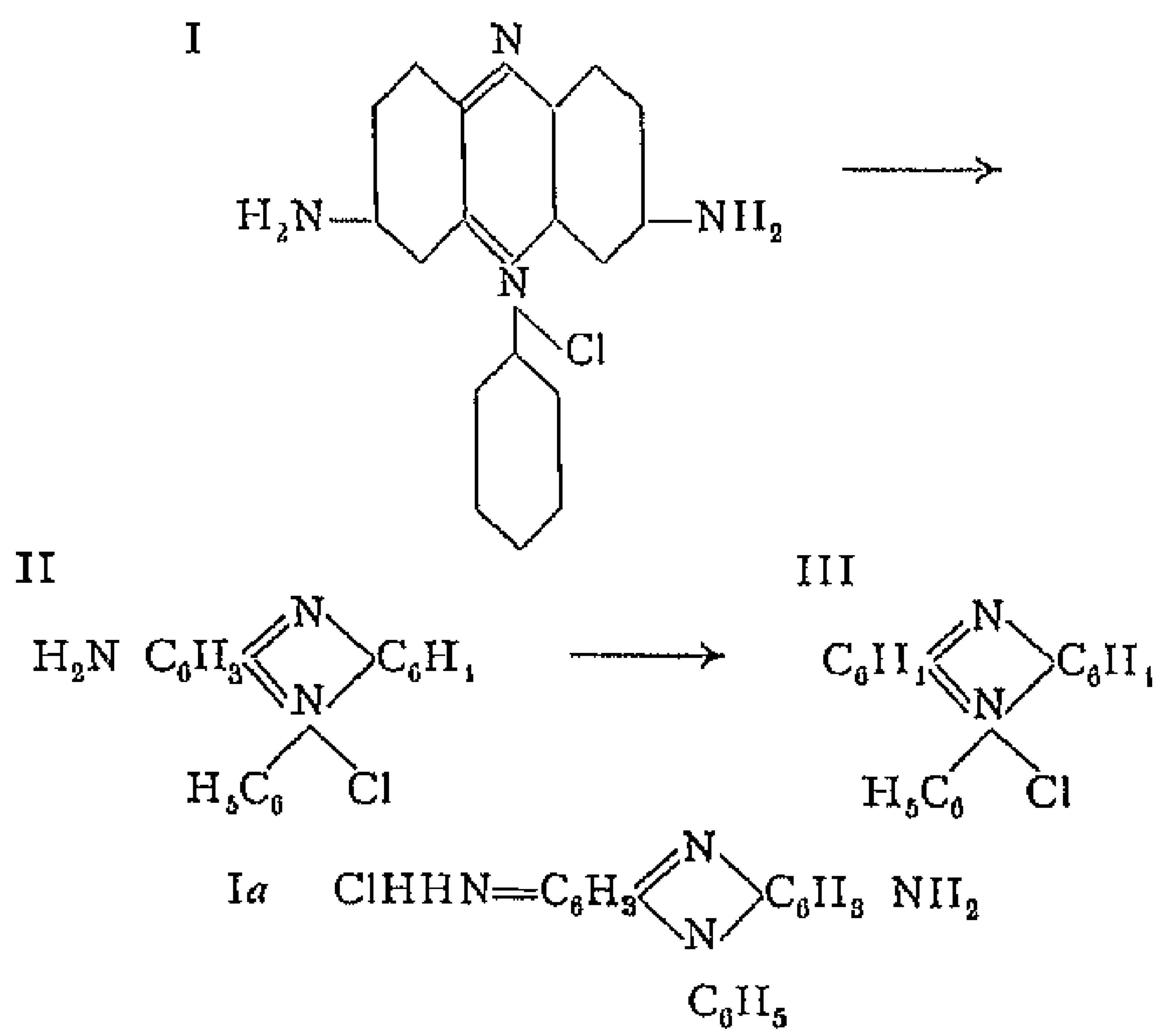
The safranines form three series of salts, monacid (red), diacid (blue) and triacid (green). Only the monacid salts are stable towards water, the others are decomposed by it. Animal fibres, as well as tannin-

[1] Nietzki, *Ber*, 1883, 16, 464; 1886, 19, 3163. Hardin, *Ber*, 1900, 33, 1212

mordanted cotton, are dyed red by the safranines. Both of the amino-groups in these compounds may be diazotised.



The *constitution of the safranines* has been solved by the work of Nietzki[1] and Kehrmann. **Phenosafranine**, the simplest member of the group, has been shown to be the phenyl-ammonium derivative of symmetrical diamino-phenazine. Its hydrochloride is represented as in formula I. When the diazonium compound of this base is heated with alcohol, one amino-group is eliminated and **aposafranine** (II.) is formed. In a similar manner the diazonium derivative from the latter may be converted into phenyl-phenazonium chloride (III.).

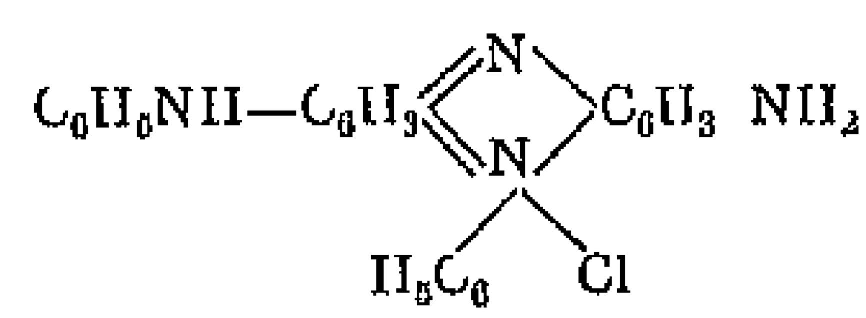


Formula I*a* was proposed for safranine on the ground that the amino-groups could be eliminated from its molecule separately. This formula, which contains a para-quinonoid structure, has been the subject of much controversy, and is now obsolete.

[1] Nietzki, *Ber.*, 1896, **29**, 1442. Kehrmann, *ibid.*, 2316.

The safranine of commerce consists chiefly of **tolusafranine**, $C_{21}H_{20}N_4HCl$. It is prepared by oxidising a mixture of one molecule of *p*-toluylene diamine and two molecules of *o*-toluidine by means of potassium bichromate or manganese dioxide. *p*-Toluylene diamine, $C_6H_3(CH_3)(NH_2)_2$, is obtained by the reduction of amino-azotoluene, which in turn is prepared from *o*-toluidine. Safranine dyes tannin-mordanted cotton a scarlet red and silk a fine rose tint, but these shades are not fast to light.

Mauveine, the first aniline dye stuff to be prepared industrially, is of great historical interest. It was obtained by Perkin in 1856, by the oxidation of crude aniline, and consists of a mixture of phenylated safranine,

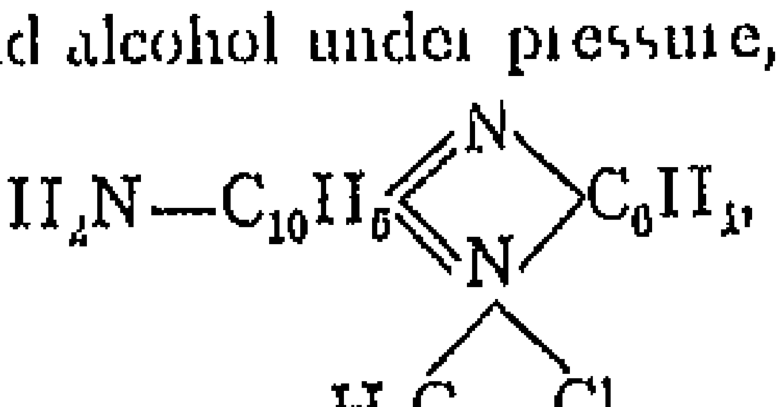


and its homologues.

Magdala red, $C_{30}H_{21}N_4Cl$, was at one time extensively used. It is a safranine of the naphthalene series.

Aposafranines

Aposafranine, which is formed by the elimination of one amino-group from phenosafranine (see p. 744), is a typical member of a comparatively large group of dyes. In this group are now included many compounds formerly classed as indulines, such as the rosindulines and iso-rosindulines, both of which contain a naphthalene nucleus. In the *rosindulines* the amino-group is present in the naphthalene nucleus, and in the *iso-rosindulines* in the benzene nucleus (O. Fischer and Hepp).

Rosinduline is prepared by heating benzene-azo-α-naphthylamine with aniline and alcohol under pressure, and also by other methods. Its hydrochloride, , is a red dye. The disulphonic acid dyes a yellowish red shade. Eighteen structural isomerides of rosinduline are known, in which the amino-group occupies different positions in the naphthalene, benzene, or N-phenyl nucleus.[1]

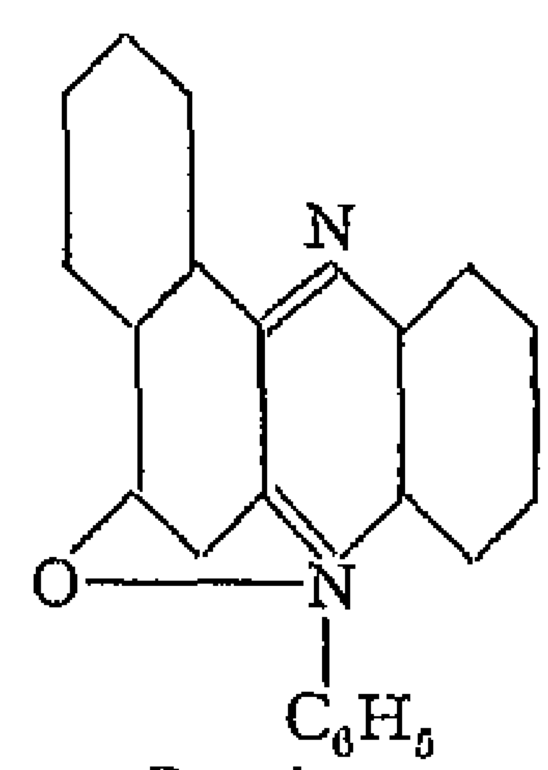
Phenyl-rosinduline, a derivative in which the amino-group of rosinduline is phenylated, is obtained by heating benzene-azo-α-naphthyl-

[1] Kehrmann and collaborators, *Ber.*, 1897, 30, 2632; 1898, 31, 3097; 1899, 32, 927, 2627; 1900, 33, 1543, 3276; 1901, 34, 1225, 3097; *Ann.*, 1896, 290, 275; *Helv. Chim. Acta*, 1925, 8, 655.

amine with aniline and aniline hydrochloride Its disulphonic acid is used commercially as a red dye-stuff for wool, under the name of **azocarmine**

When safranines and aposafranines are heated with alkali or concentrated hydrochloric acid, the amino-groups are replaced by hydroxyl groups The reaction is accompanied by a simultaneous isomerisation into the *p* quinonoid or internal salt structure, and leads to the formation of safranols, safranones and rosindones

Rosindone is obtained in this way by heating rosinduline with concentrated hydrochloric acid



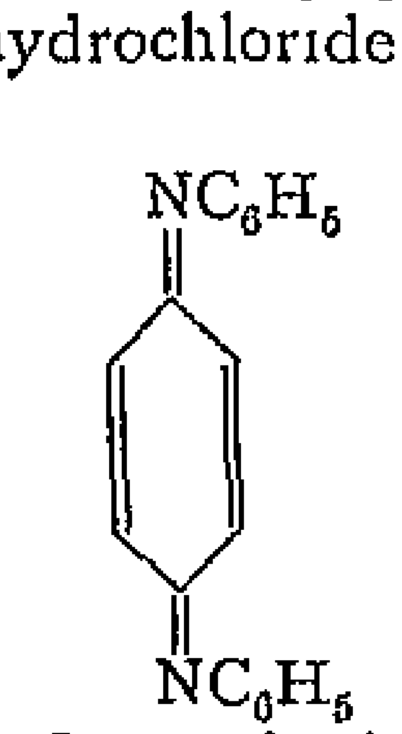
Rosindone

Rosinduline G is a sulphonic acid of rosindone, and is used as a red acid dye

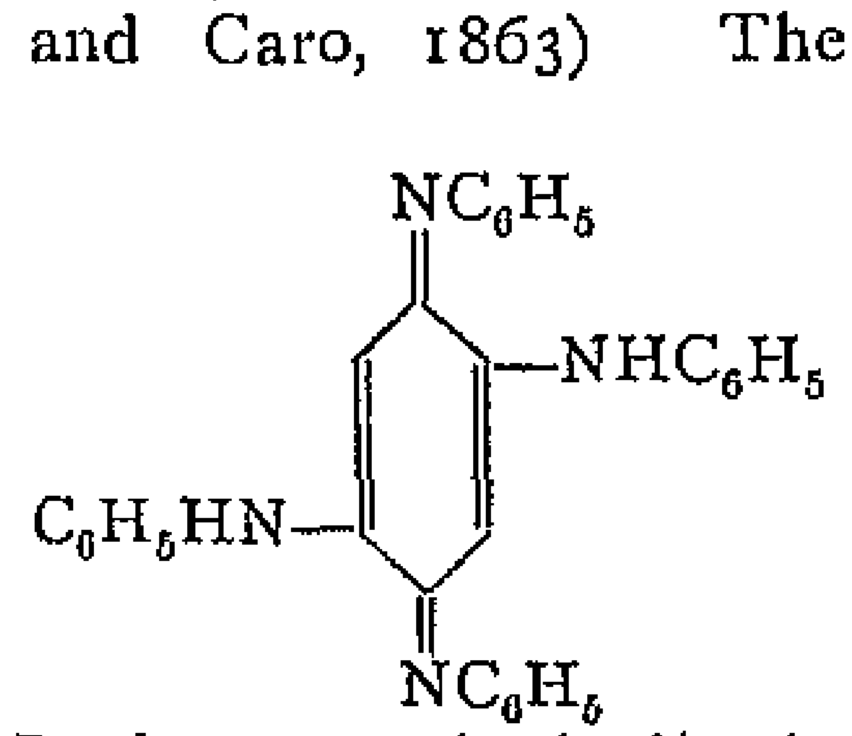
Indulines

The indulines, the first example of which was prepared in 1863 by Dale and Caro, give shades resembling those of indigo blue They occur as by-products in the "magenta melt," and are prepared by heating aminoazo-benzene with primary aromatic amines and their salts (induline melt)

Induline, $C_{30}H_{23}N_5$, is prepared by heating aminoazo-benzene with aniline hydrochloride (Dale and Caro, 1863) The intermediate



Quinone dianil



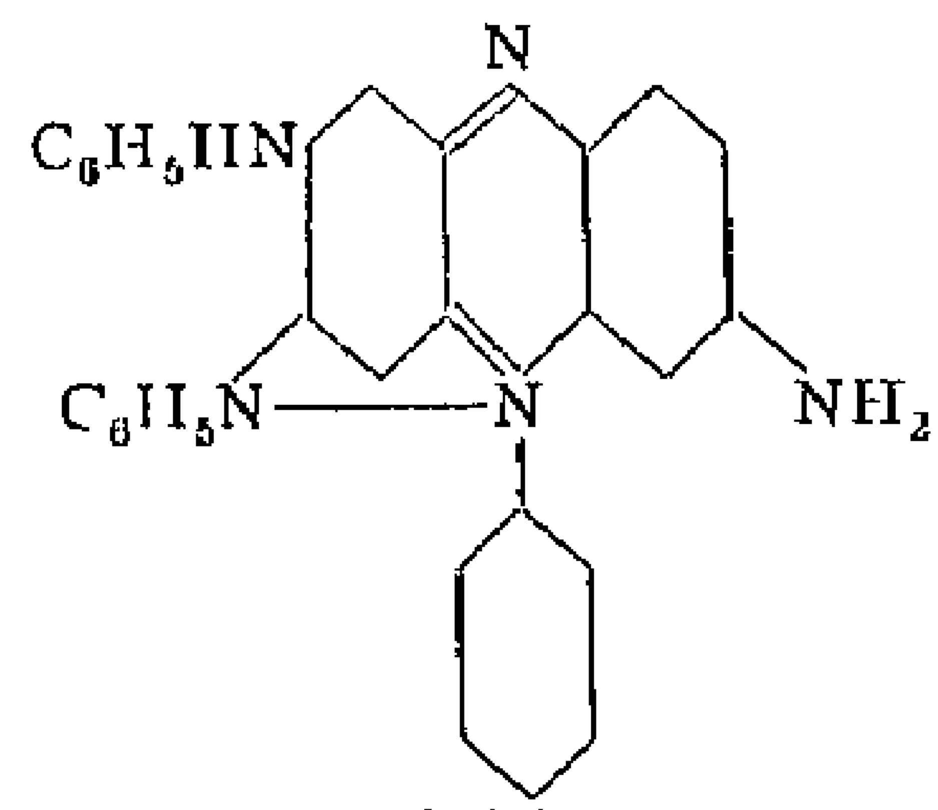
2 5 Dianilino-quinone dianil (Azophenine)

compounds in this reaction have been shown to be quinone dianil and 2 5-dianilino-quinone dianil, or *azophenine*

O Fischer and Hepp have proved that induline has the annexed formula

Some of the most important indulines have been synthesised by Kehrmann [1]

Induline gives reddish violet salts which are soluble in water, and are used directly on tannin-mordanted cotton



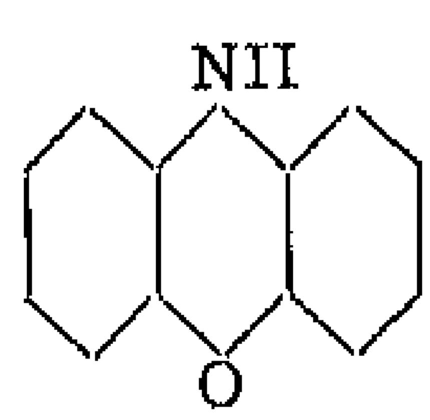
Induline

On heating the dye with aniline and aniline hydrochloride, more phenyl and amino-phenyl groups enter the molecule, with the formation of complex indulines These are insoluble in water and are used either in alcoholic solution (spirit indulines), or in the form of their water-soluble sulphonic acids, for dyeing wool Cotton may be dyed with the aid of *acetin*, a mixture of glyceryl esters of acetic acid, which acts as a solvent For this purpose, induline is made into a paste with tannin and acetin, and printed on to the material The acetin dissolves the dye and ensures the formation of the tannin lake On subsequent treatment with steam, the acetin is hydrolysed to glycerol and acetic acid and the lake is deposited on the fibres

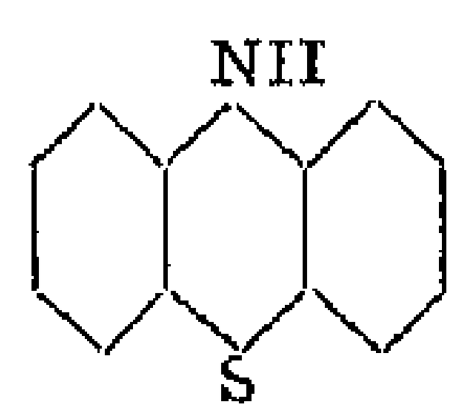
Aniline black is a very valuable dye which is formed when aniline is oxidised by various reagents (such as sodium and potassium chlorates in presence of copper and vanadium compounds) It is always produced directly on the fibre and is widely employed in calico printing and cotton dyeing, but is not much used for wool It is an amorphous, violet black powder, which is insoluble in water and alcohol, is strongly basic and forms green, unstable salts with acids The constitution of aniline black is still unknown Its composition is probably represented by $C_{30}H_{27}N_6$

III—OXAZINE (AZOXINE) AND THIAZINE (THIONINE) DYES [2]

These compounds contain a nucleus built up of four carbon atoms, a nitrogen atom, and, according as they are derived from phenoxazine or phenthiazine, an atom of oxygen or sulphur



Phenoxazine



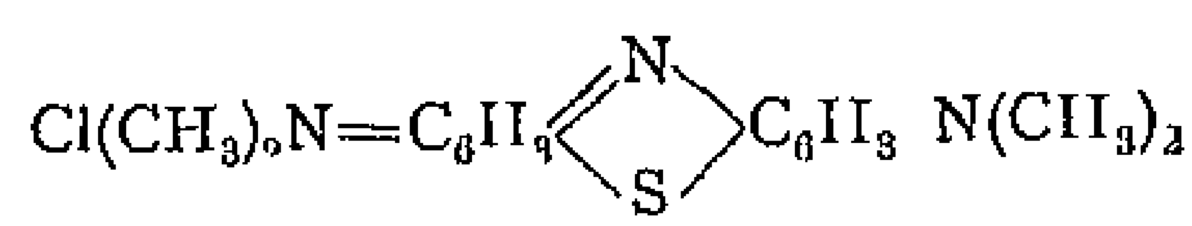
Phenthiazine, Thio diphenylamine

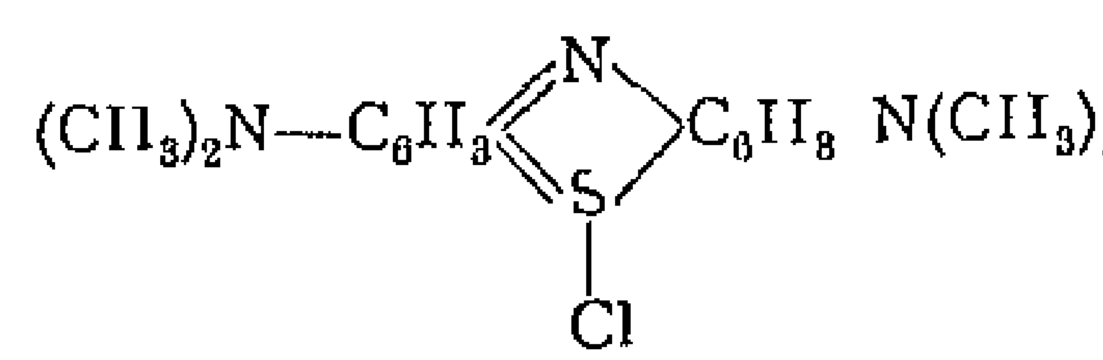
The amino and hydroxy derivatives of these parent substances are leuco-compounds, which on oxidation give the corresponding dyes

[1] F Kehrmann, *Ber*, 1923, 56, 2391 [2] Kehrmann, *Ann*, 1902, 322, 1, *Ber*, 1906, 39, 914 A Hantzsch, *Ber*, 1905, 38, 2143, 1906, 39, 153, 1365

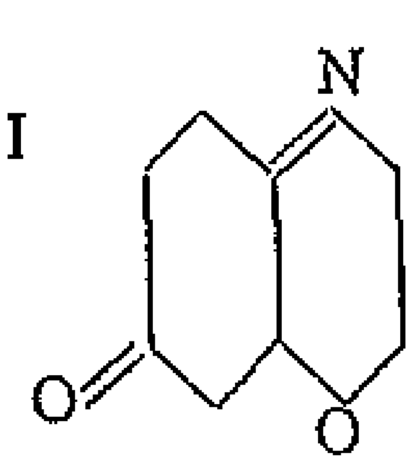
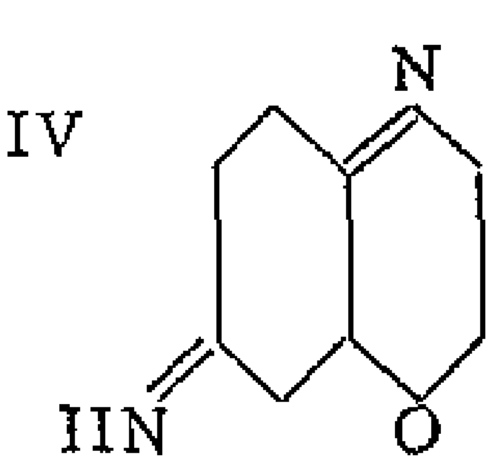
Phenoxazine crystallises in plates, m.p. 148°, and is prepared by fusing *o*-amino-phenol with catechol.

Two suggestions have been put forward as to the constitution of dyes of this class containing an ammonium grouping. The older view of Bernthsen, O. Fischer and others, which is adopted here, is that they are quinonoid ammonium salts.[1] Kehrmann, however, regards them as oxonium and thionium salts. The two types of formulæ may be illustrated in the case of *methylene blue*.

I. Ammonium formula 

II. Thionium formula 

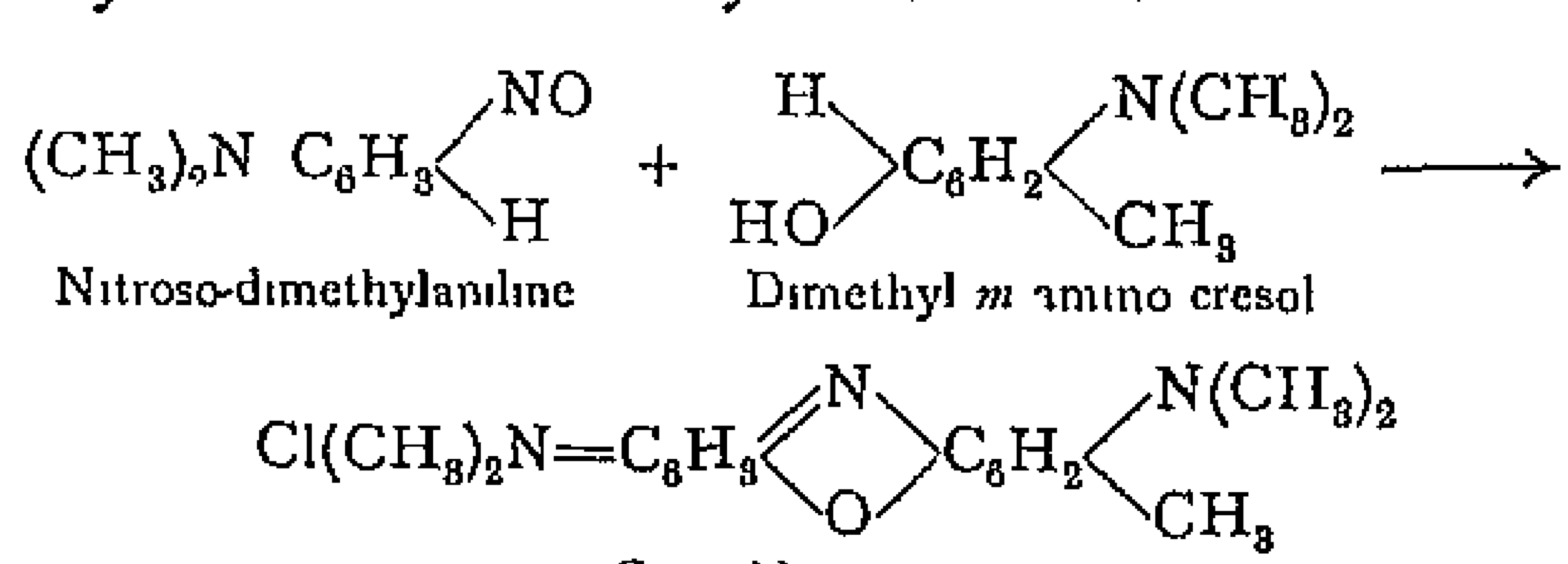
With regard to the nomenclature of these compounds, all dye-stuffs containing the complex III, such as gallocyanin, are grouped together under the name of *oxazones*. Other dyes, such as Capri blue, contain a quinone imine structure (IV), and are known as *oxazimes*. The corresponding sulphur derivatives are termed *thiazones* and *thiazimes*.

III  IV 

The chromophore present in such compounds is not the oxazine or thiazine ring, as is sometimes assumed, but the paraquinonoid grouping.

These dye-stuffs are prepared by the condensation of nitroso-dimethylaniline, nitroso-phenols, or quinone dichloro-imines with tertiary amino-phenols or polyhydric phenols.[2]

In this way, the dye **Capri blue** is obtained by the interaction of nitroso-dimethylaniline and dimethyl-*m*-amino-cresol.



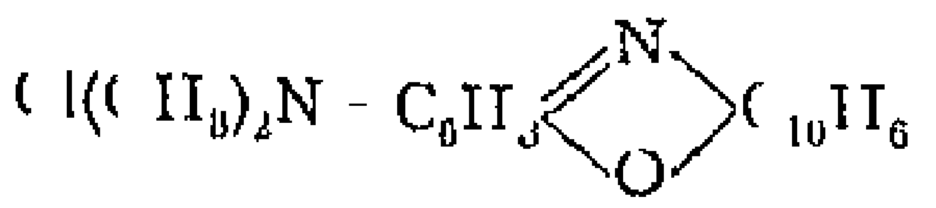
Capri blue

[1] A. Bernthsen, *Ch. Zeit.*, 1908, 82, 956.

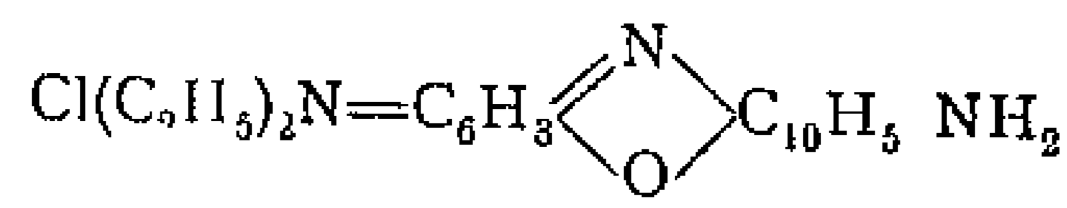
[2] See also A. Fairbourne and H. Toms, *J.C.S.* 1921, 119, 2076.

Meldola's blue (*naphthol blue*, *new blue R*, *fast blue*), which dyes tannin-mordanted cotton a violet blue shade, is prepared by the action of nitroso-dimethylaniline on β-naphthol Its constitution is represented by formula V

V

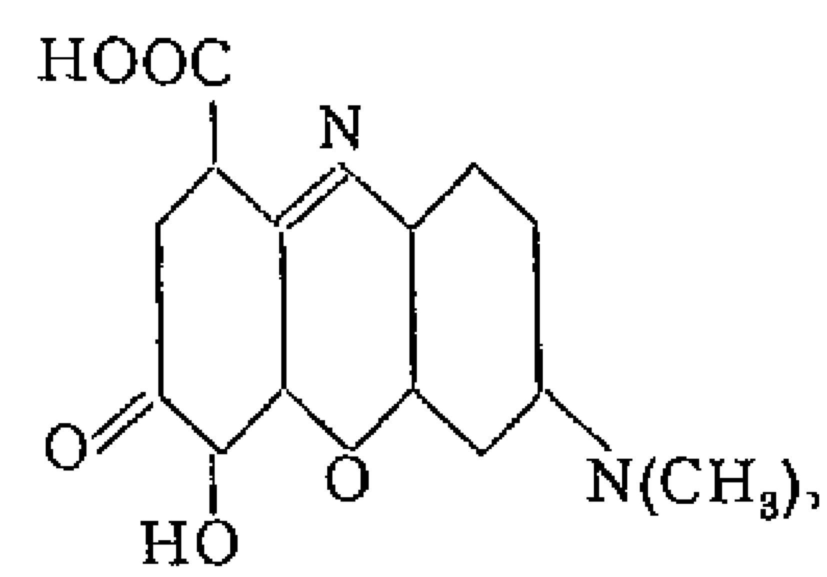


VI



Nile blue, formula VI, is prepared by the action of nitroso diethyl *m*-aminophenol on α-naphthylamine It dyes silk and tannin-mordanted cotton a greenish blue shade

Gallocyanin is formed by the action of nitroso dimethylaniline on gallic acid It is a carboxylic acid of the annexed formula

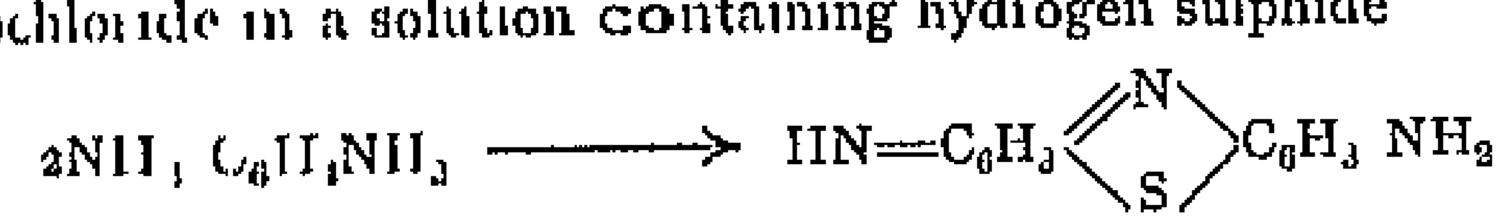


Gallocyanin is a mordant dye, which gives a fine blue-violet lake with chromium oxide It is largely used in calico printing

On heating gallocyanin with aniline, the carboxyl group is replaced by the group NHC_6H_5 When the latter is sulphonated by heating the compound with concentrated sulphuric acid, a sulphonic acid is obtained which is used commercially under the name of *Delphine blue*

Phenthiazine, *thio-diphenylamine* (see p 747), is also the parent compound of a number of dye-stuffs It melts at 150°, boils at 370°, and is prepared in an analogous manner to phenoxazine by heating *o* amino-thiophenol with catechol, or more conveniently by heating diphenylamine with sulphur or sulphur chloride The introduction of amino groups into phenthiazine leads to the formation of leuco-compounds, which on oxidation yield dyes These were first prepared by Lauth by the oxidation of *p*-diamines in the presence of hydrogen sulphide *Methylene blue* is the most important member of this group

Lauth's violet, *thionine*, *amino phenthiazine*, is prepared by oxidising *p* phenylene diamine hydrochloride in a solution containing hydrogen sulphide



The aqueous solution of its hydrochloride is violet in colour

Methylene blue, $Cl(CH_3)_2N=C_6H_3\langle{}^{N}_{S}\rangle C_6H_3N(CH_3)_2$, was discovered in 1876 by Caro, who obtained it by oxidising dimethyl-*p*-phenylene diamine in presence of hydrogen sulphide It may be

prepared on a large scale by the reduction of *p*-nitroso-dimethylaniline with hydrogen sulphide in strongly acid solution, followed by oxidation of the resulting amino compound with ferric chloride in the presence of hydrogen sulphide During this reaction, one atom of sulphur enters into combination with two molecules of the amino compound, and one atom of nitrogen is eliminated as ammonia In modern practice the sulphur is introduced by means of sodium thiosulphate The oxidation of dimethyl-*p*-phenylene diamine, in the presence of sodium thiosulphate, results in the formation of the thiosulphonic acid of the base, $C_6H_3[N(CH_3)_2](NH_2)(S\ SO_3H)$ The latter, on being mixed with dimethylaniline and subjected to further oxidation, yields the corresponding indamine thiosulphonic acid, which when boiled with dilute acid parts with sulphuric acid to give methylene blue [1]

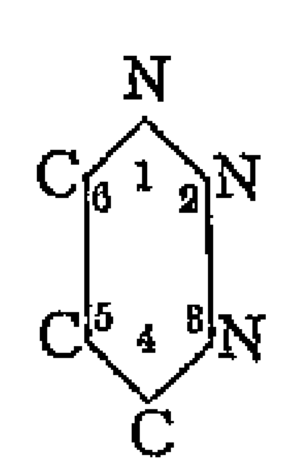
The dye is precipitated from aqueous solution by the addition of zinc chloride and common salt, and is placed on the market in the form of its zinc chloride double salt The latter is very soluble in water It does not dye wool readily but is used for silk and tannin-mordanted cotton, the colour being very fast to light It is the most important of all the blue basic dyes, and is widely used in calico-printing and cotton-dyeing

Methylene azure is produced by the oxidation of methylene blue in dilute acid solution (*e g*, potassium dichromate and sulphuric acid), when the N-methyl groups are partially replaced by hydrogen [2]

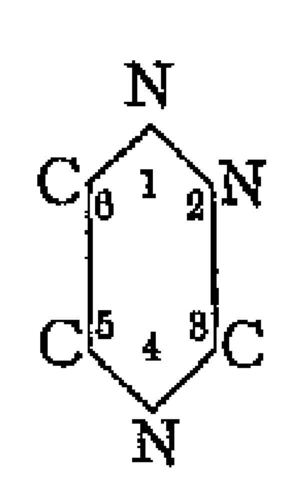
When treated with nitrous or nitric acid, methylene blue yields a dark green colouring matter which is probably a mononitro derivative of methylene blue This is known as **methylene green** and dyes a dark green colour

IV —TRIAZINES

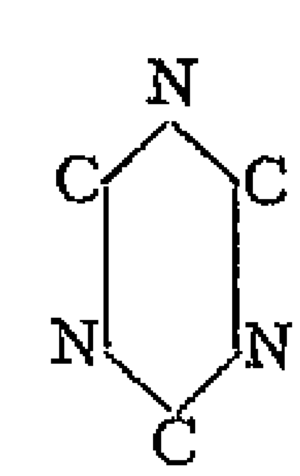
Three different six-membered rings composed of three nitrogen and three carbon atoms are theoretically possible Derivatives of all three types are known



Vicinal triazines, β triazines



Asym triazines, α triazines

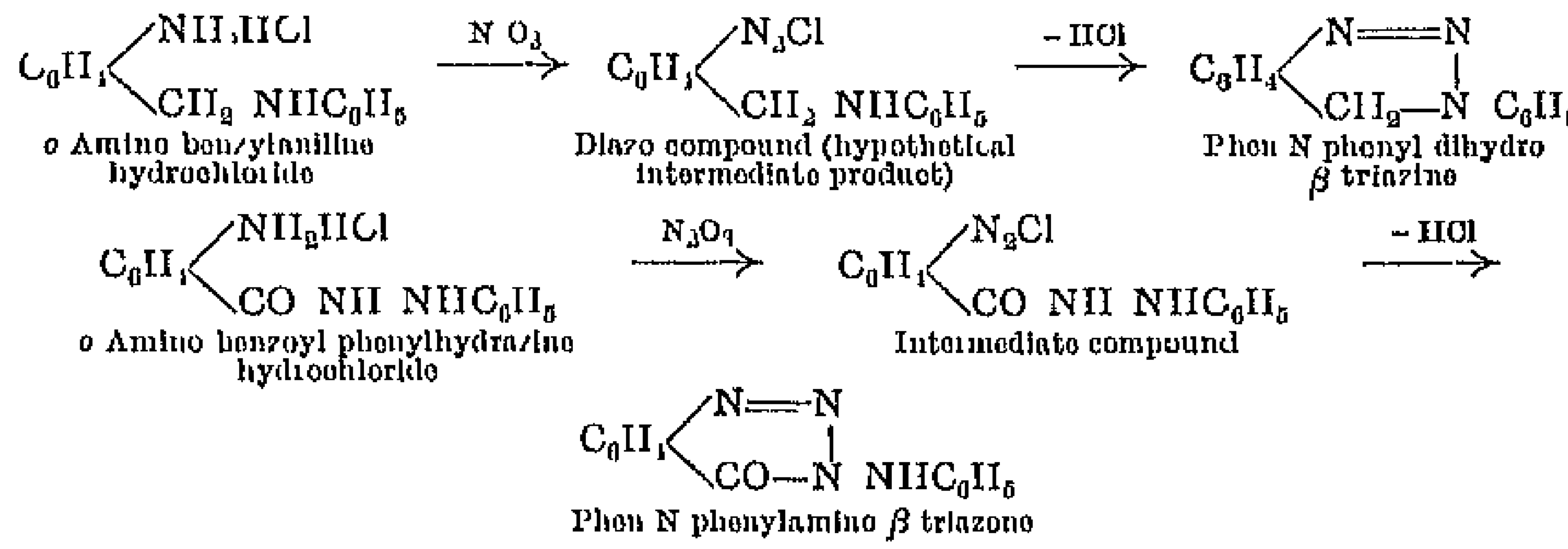


Sym triazines, cyanidines

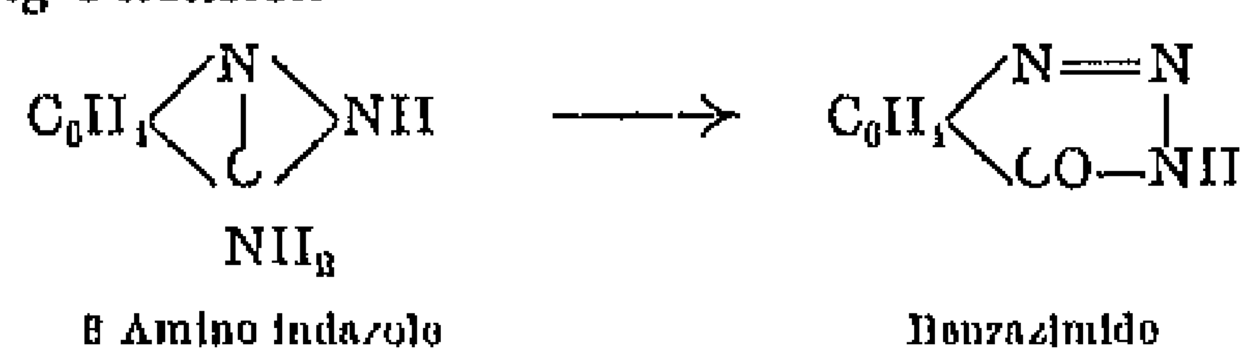
[1] Bernthsen, *Ann*, 1885, **230**, 73, 1889, **251**, 1 Bernthsen, *ibid*, 1804

[2] Kehrmann, *Ber*, 1906, **39**, 1405

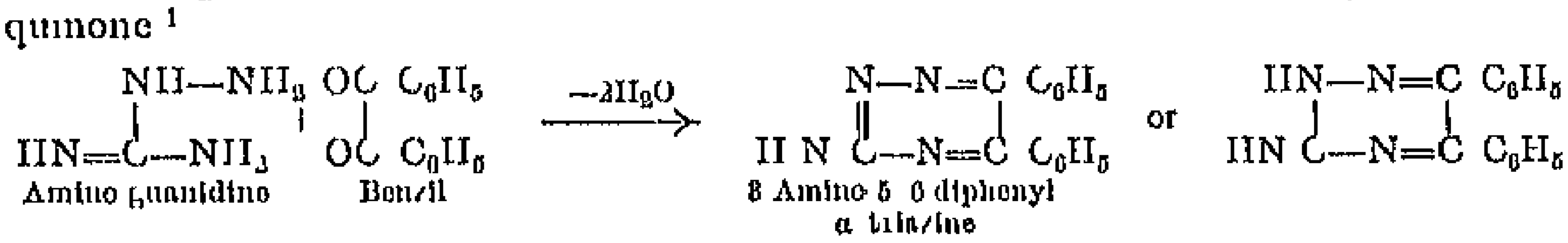
Derivatives of vicinal or **β triazine** are prepared by the action of nitrous acid on *o* amino benzylamine bases,[1] or on *o* amino benzoyl phenylhydrazine,[2] a reaction which probably results in the intermediate formation of diazo compounds, *e g*,



Benzazimide, a member of this series, is formed by the action of nitrous acid on the amide of anthranilic acid, and also by the oxidation of 3 amino indazole, as the result of ring extension [3]

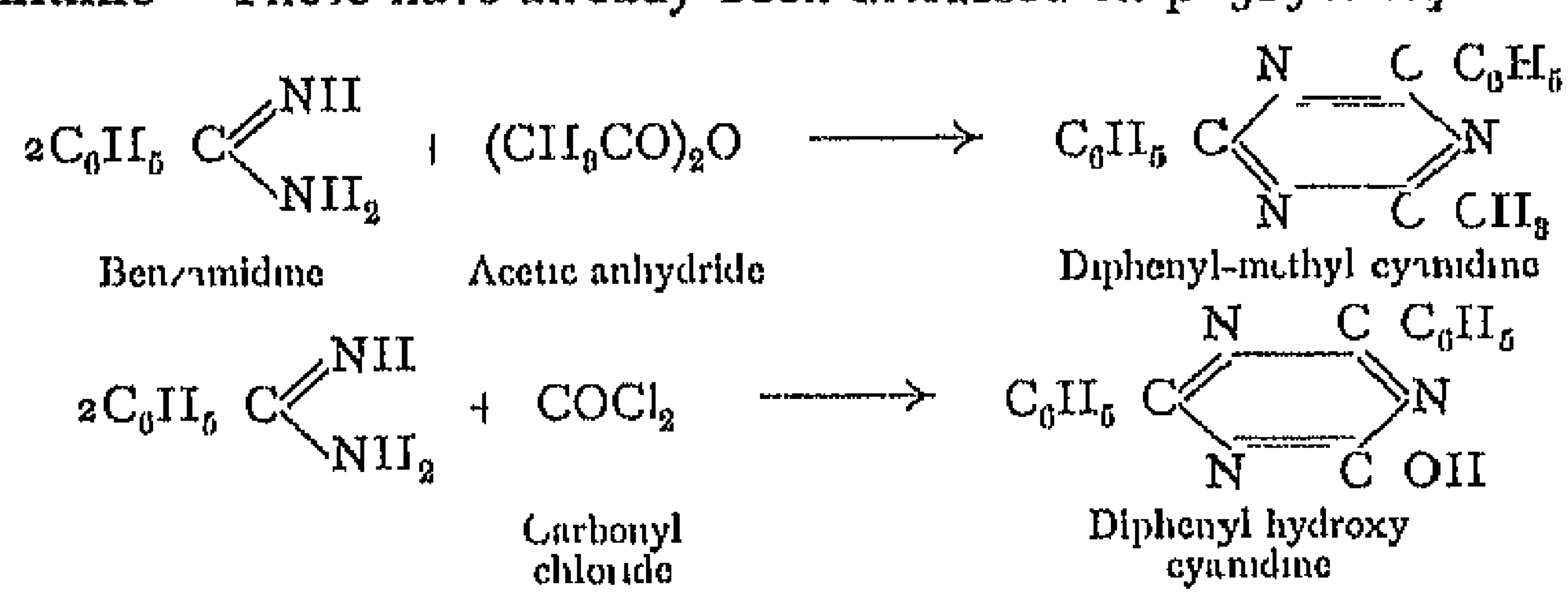


Derivatives of asymmetrical or **α triazine** are obtained by the condensation of amino guanidine with aromatic α diketones, such as benzil and phenanthra quinone [1]



It has not yet been decided whether the amino or the imino-formula best represents the constitution of these compounds Probably the systems are tautomeric They have very little basic character and are not affected by nitrous acid Potassium hydroxide converts diphenyl aminotriazine into diphenyl hydroxytriazine

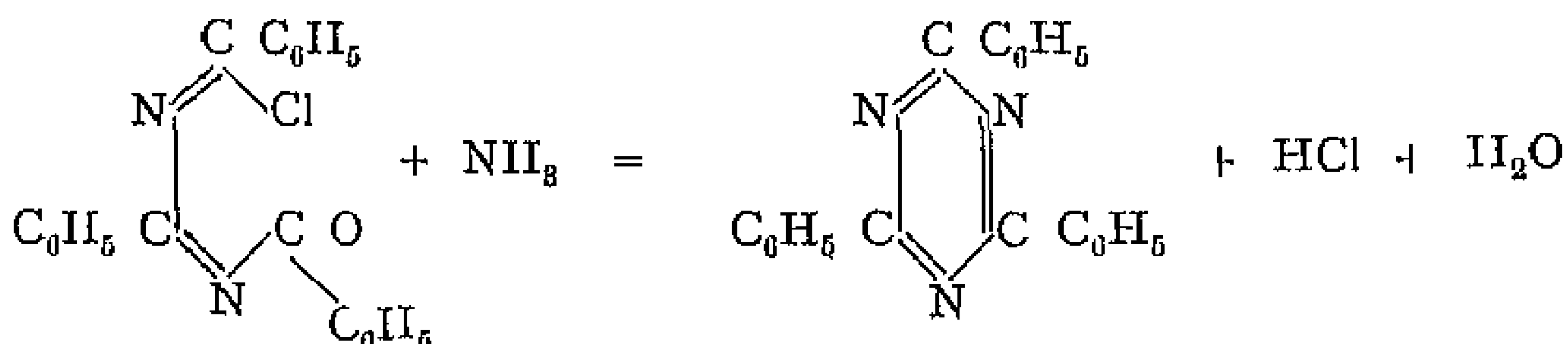
The polymeric cyanic compounds, such as cyanuric acid, cyamelide and melamine, are interesting derivatives of **symmetrical triazine** or **cyanidine** These have already been discussed on p 325 *et seq*



[1] M Busch, *Ber*, 1892, 25, 445 [2] König and Reissert, *Ber*, 1899, 32, 782 [3] Bamberger, *Ann*, 1899, 306, 289 [1] Thiele and Bihan, *Ann*, 1898, 302, 299

A general method of preparing the **cyanidines** is by the action of acid anhydrides, or of carbonyl chloride, on aromatic amidines.[1]

Many cyanidines may be obtained by the action of aluminium chloride on a mixture of benzonitrile and benzoyl chloride or a fatty acid chloride.[2] In the reaction between benzonitrile and benzoyl chloride it is advantageous to add ammonium chloride to the mixture, when cyaphenine or triphenyl cyanidine is produced in moderately good yield. This is one of the earliest known cyanidines. The reaction is probably due to the initial formation of a condensation product of benzonitrile and benzoyl chloride, which then interacts with ammonia in the following manner:

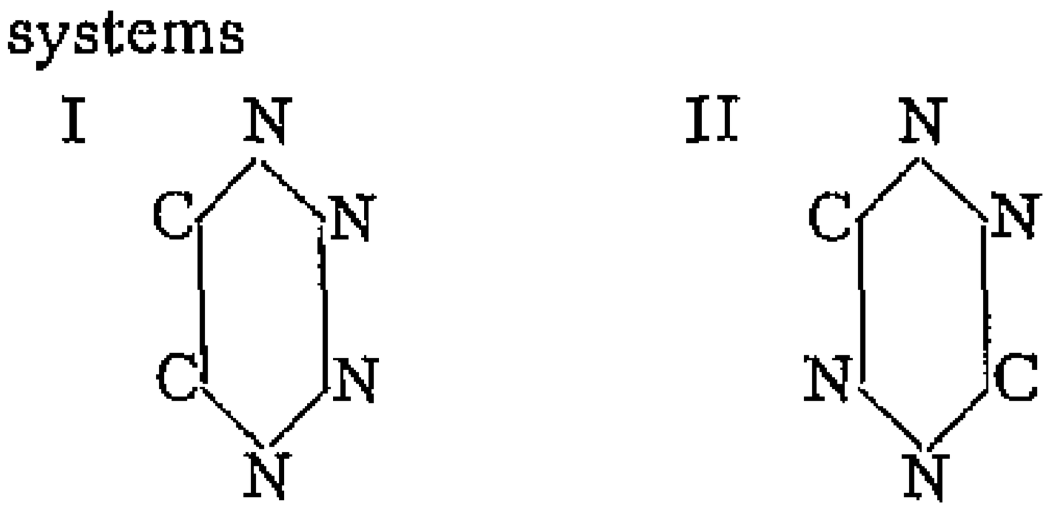


Cyaphenine

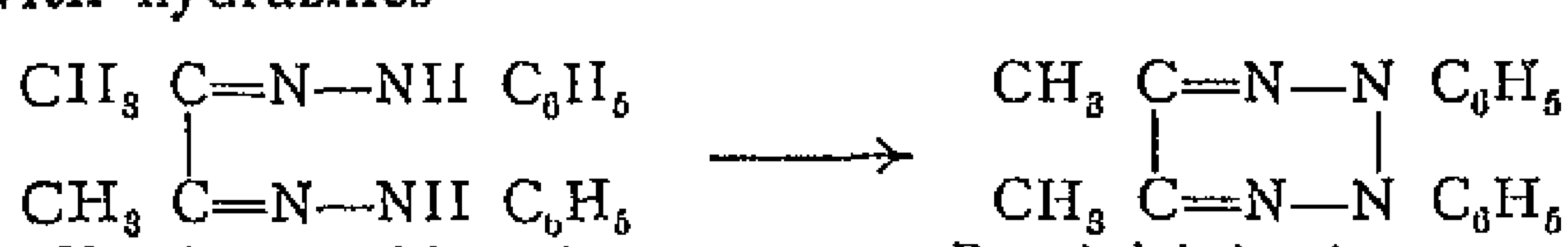
Cyaphenine crystallises in colourless needles which melt at 233°, and readily sublime. Its constitution follows from its formation by the action of sodium on a mixture of cyanuric chloride and bromo-benzene. It has no basic properties, and is decomposed by nascent hydrogen into ammonia and lophine (2 : 4 : 5-triphenyl-glyoxaline).

V.—TETRAZINES

Two isomeric series of tetrazines are known, derived from the following ring systems:



The ring system (I.) is present in the **osotetrazines**, obtained by oxidising the osazones (see p. 249) formed by the union of 1 : 2-diketones with hydrazines.[3]



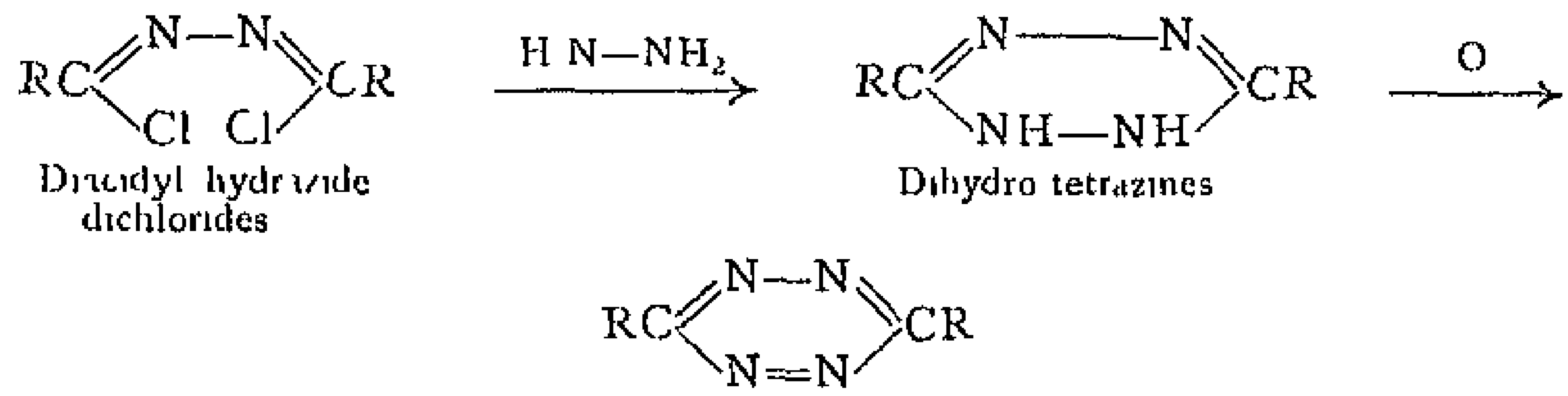
Phenylosazone of diacetyl — Dimethyl diphenyl osotetrazine

The osotetrazines are colourless neutral compounds which crystallise well. On reduction they are again converted into osazones. When

[1] Pinner, *Ber.*, 1892, **25**, 1624. [2] For the mechanism of the reaction, see Eitner and Krafft, *Ber.*, 1892, **25**, 2263. [3] R. Stollé, *Ber.*, 1926, **59**, 1743.

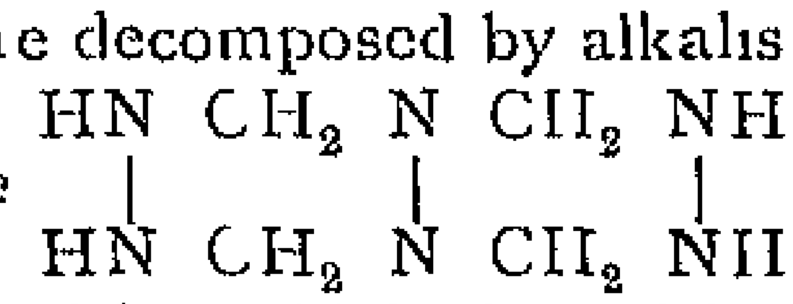
osotetrazines are warmed with mineral acids, the ring contracts with the formation of osotriazoles (see p 626) An open-chain structure is also under consideration for these compounds [1]

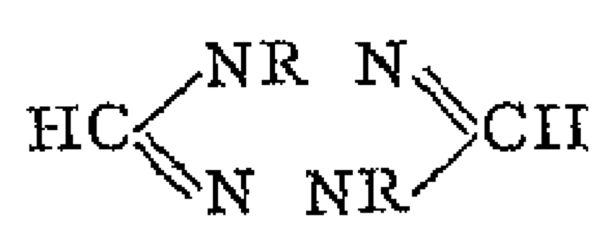
Symmetrical tetrazines containing the ring system (II) are readily prepared by the oxidation of dihydro-tetrazines, which result from the action of hydrazine on imino-ethers,[2] or on dichlorides of diacidyl hydrazides [3] Dihydro-tetrazines can also be obtained from diazoacetic ester [4]



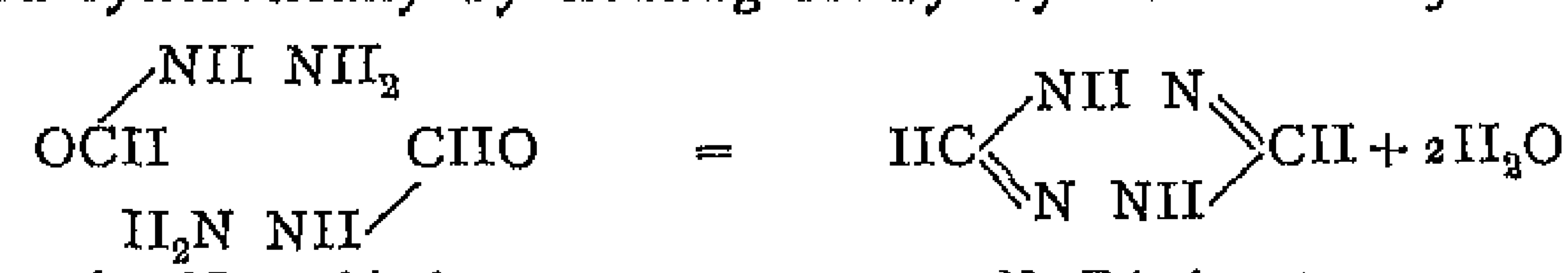
Diacidyl hydrazide dichlorides Dihydro tetrazines Sym tetrazines

The symmetrical tetrazines have a deep red colour They are stable towards acids but are decomposed by alkalis

Bis-hexahydro-tetrazine  is readily prepared from an aqueous solution of formaldehyde and hydrazine hydrate It is used in analytical chemistry as a reducing agent [5]

Compounds having a ring structure of the type 

are described as *N,s-dihydro-tetrazines* or *isodihydro-tetrazines* The parent compound, **N,s-dihydro-tetrazine** or isodihydro-tetrazine, is prepared synthetically by heating formyl-hydrazine at 150° to 200°,



2 mols of Formyl hydrazine N,s-Dihydro tetrazine

and also from the polymerisation products of diazo-acetic ester (p 217)

These interesting polymerisation products, which are themselves tetrazine derivatives, have been extensively investigated by Hantzsch and Silberrad [6]

N,*s*-Dihydro-tetrazine and its derivatives behave as weak monacid bases, the C-dimethyl and diethyl compounds being more basic than the unsubstituted product [7] The ring is readily ruptured with the production of hydrazines

[1] D Vorlander, *Ber*, 1927, 60, 849 [2] Pinner, *Ann*, 1897, 297, 238 [3] R Stollé, *J pr Ch*, 1906, [2], 73, 277 [4] Curtius, Darapsky und E Müller, *Ber*, 1908, 41, 3161, 1909, 42, 3284 [5] K A Hofmann und D Storm, *Ber*, 1912, 45, 1725 [6] *Ber*, 1900, 33, 58 [7] Hantzsch and Silberrad, *loc cit* Dedichen, *Ber*, 1903, 36, 1831

IX

Proteins[1]

From the investigations of Emil Fischer, proteins may be defined as naturally occurring substances of high molecular weight, which are largely composed of amino-acid residues united together by an amide type of linking. Other types of units and other modes of union may also be present (see p 774)

These substances are of great biological interest, since they include some of the most important constituents of the living cell. So intimately are they bound up with the processes of life, that each type of organism, and each kind of cell within the organism, possesses its own characteristic proteins. In fact, in the higher organisms, foreign proteins often act as strong poisons when introduced directly into the blood-stream, instead of by way of the intestinal canal. On these phenomena are based the serological methods of modern medicine. Such reactions of the organism provide a much more sensitive means of identifying individual proteins than any chemical method. In addition, it may be noted that the physico chemical state in which the protein is present has a great influence on the activity of the cell.

A certain amount of the protein in living organisms is continually being used up in vital processes (*e g*, gland secretions), and it is necessary for the loss to be replaced. For this purpose plants utilise inorganic nitrates as their main source of nitrogen. The animal body is incapable of building up all the requisite constituents of protein molecules from nitrates and non-nitrogenous organic substances, such as carbohydrates and fats, and consequently makes use of ingested protein to replace the loss. Protein is therefore an essential constituent of animal diet. At one time it was considered that proteins were, in themselves, sufficient to maintain life, and that the most satisfactory and economical diet was one containing the highest possible proportion of protein. This has been disproved, however, by recent investigations on nutrition. Moreover, different proteins are not utilised by the organism to the same extent[2]. The older method of regarding the problem of nutrition, as being primarily

[1] For further information reference may be made to the following sources —*The Chemical Constitution of the Proteins*, Parts I and II, by R H A Plimmer (Longmans), *The Vegetable Proteins*, by T B Osborne (Longmans, 1924), *The General Character of the Proteins*, by S B Schryver (Longmans), *Colloid Chemistry of the Proteins*, by Pauli, translated by Thorne (Churchill, 1922), *Chemie der Eiweisskörper*, by O Cohnheim (Vieweg, Braunschweig), "Untersuchungen über Aminosäuren, Polypeptide und Proteine," by E Fischer, *Ber*, 1906, 39, 530. Sorensen, *J C S*, 1926, 2995. [2] See, for example, Berczeller, *Biochem Zeitsch* 1922, 129, 217

dependent on the energy content of the food, had therefore to be modified, and more attention paid to the chemical nature of the diet

At the outset it should be emphasised that the chemical investigation of the proteins is attended with very great difficulty This is due, on the one hand, to the complexity of the protein molecule, and on the other, to the fact that the usual methods of isolation fail to give pure homogeneous compounds The chief criterion of the purity and uniformity of a solid substance is its power of crystallisation As will be seen later, this test can only be applied to the proteins in a very limited sense The usual method of purifying a liquid compound is by distillation, but no protein can be distilled without decomposition Hence the study of their physico-chemical properties is of the highest importance in the chemical and physiological investigation of these compounds

Proteins are colloids and do not diffuse through animal membranes This property is used in their purification They occur in complex mixtures from which they are usually isolated by salting out Owing to their colloidal nature, the proteins so prepared retain adsorbed crystalloids, especially electrolytes, which are exceedingly difficult to remove After months of dialysis under aseptic conditions, Pauli succeeded in preparing a protein solution practically free from electrolytes Sorensen,[1] after prolonged dialysis through collodion membranes, was able to obtain protein solutions with reproducible properties, but having a definite, although extremely low, content of ammonium sulphate

In the properties already described, proteins resemble the *hydrophobe* or *suspensoid colloids* of inorganic chemistry (*e g*, colloidal metals) In other respects, however, they exhibit differences which led to them being classed with certain other colloids as *hydrophile* or *emulsoid colloids* Largely through the work of Pauli, Michaelis and Sorensen—and in opposition to the views of Ostwald—this idea has undergone further extension The properties of natural[2] proteins are not regarded as being explicable solely from the standpoint of colloid chemistry, and the compounds are therefore supposed to occupy an intermediate position between the suspensoids and crystalloids

The inability of the proteins to diffuse through animal membranes shows that they have a high molecular weight Nevertheless, protein solutions possess a measurable, though very small, osmotic pressure Sorensen, who has carried out the most recent and accurate investigations on purified egg albumin, found that the osmotic pressure[3] of the protein was constant for solutions of a definite composition This

[1] S P L Sörensen and Höyrup, *Z physiol Ch*, 1918, 103, 15 [2] That is, not denatured (see p 756) [3] It is doubtful whether true values of molecular weight are indicated in such osmotic pressure measurements

shows that it is possible to reproduce protein solutions containing particles of a definite size

The addition of alkali salts to a protein solution causes a gradual decrease in the osmotic pressure, and at a definite concentration of the salt the protein is precipitated During such a precipitation the protein retains its original properties, and, after having been filtered off, may be brought into solution again in its original condition This method of *reversible precipitation by neutral salts*, which was introduced by Hofmeister, is used for the isolation of certain kinds of proteins It differs from the precipitation of suspensoid colloids by electrolytes, in that the proteins are only precipitated by a much higher concentration of the salt As was first shown by Hofmeister, neutral salt precipitation depends on the specific action of the ions of the salt According to Pauli, cations generally tend to assist and anions to retard precipitation The relative influence of the ions may be expressed by arranging them in the following "lyotropic" series[1] The order in which cations assist precipitation is $Li<Na<K<NH_4$, whilst that in which anions retard precipitation is $CNS<I<Br<NO_3<Cl<CH_3COO<HPO_4<SO_4$

In acid media the above order is reversed It must be remembered, however, that the factors governing precipitation are very complex, and, like most of the laws of protein chemistry so far discovered, the above can only be regarded as a broad generalisation

It has recently been proved by Pfeiffer that neutral salts affect the solubility of amino acids in the same way as that of the proteins, and that the alteration in solubility is due to complex salt formation[2] Hence, during the precipitation of proteins by electrolytes, it is very probable that combination takes place between the neutral salt and the protein

On the other hand, a precipitation process of a different nature is undergone by protein solutions under the influence of heat, or on addition of certain substances such as alcohol, acetone, solutions of salts of the heavy metals and alkaline earths, etc For example, when a solution of a protein is heated, the protein becomes coagulated at a definite temperature, which varies with the nature of the protein and the other products present The insoluble *coagulated protein* is said to be *denatured*, and cannot be reconverted into the original compound This property is used in removing proteins from a solution, and for their quantitative estimation Physiological solutions can be freed from protein by means of mercuric chloride and hydrochloric acid (Schenck), and the quantitative estimation of protein is based on its precipitation by alcohol, acetone, tannic acid, or the action of heat

[1] This lyotropic series has also an important bearing on many biological processes, see Abderhalden's *Lehrbuch*, vol ii, p 173 [4th edition] [2] P Pfeiffer, *Organische Molekülverbindungen*, p 106 (Stuttgart, 1922)

In the precipitation of proteins by heat, it is necessary to distinguish between *denaturation* and the precipitation or *flocculation*[1] *of the denatured particles*. Protein particles which have been denatured by heat possess the properties of suspensoids. While denaturation is a process of unknown character, flocculation is a physico chemical process and will be more fully discussed.

Coagulation of protein by heat is impeded by strong acids and alkalis, owing to denaturation by the formation of *acid or alkali albuminates*. These albuminates are no longer precipitated on heating. They are insoluble in water or sodium chloride solution, but readily dissolve in dilute acid or alkali. From acid solution they are precipitated by the addition of sodium chloride. In most other respects the acid and alkali albuminates form two quite distinct groups of substances.

The heat coagulation of proteins is also modified by the presence of salts. In general, small quantities of salts retard coagulation, and hence the coagulation temperature (*i.e.*, the lowest temperature at which coagulation takes place) is raised; larger quantities, on the other hand, assist the separation of protein. Consequently, in order to obtain as complete a coagulation as possible under the influence of heat, the protein solution is usually treated with neutral salts. Here again, however, the influences at work are of great complexity.

The properties of a protein solution depend to a large extent on the concentration of hydrogen ion present, and recent research on these compounds has been largely concerned with this question. Owing to their basic and acidic groups, the proteins, like the amino acids, are amphoteric electrolytes, and exist in aqueous solution in the form of undissociated molecules, anions and cations. It is assumed that hydrogen ions may be produced not only from the carboxyl groups in the protein molecule but also from other sources, *e.g.*, by the enolisation of peptide groups

$$—CH_2 \cdot CO \cdot NH— \longrightarrow —CH_2 \cdot C(OH) \cdot N—$$

The dissociation constants of these acidic and basic groups are very small, most protein solutions being very slightly acid in character. As might be expected, the addition of small amounts of strong acids or alkalis leads to salt-formation and considerably increases the ionisation. Salts of proteins with weak acids and bases, on the other hand, are hydrolytically dissociated. According to Pauli, proteins are polybasic acids and polyacidic bases, but the valency of the ions is very difficult to determine. A solution of protein and alkali, for example, contains a mixture of protein ions of different valency, which varies with the amount of alkali added. Up to a limiting value, the valency increases

[1] H. Eilers and M. Landauer, *Z. ang. Ch.*, 1922, 469. W. C. M. Lewis, *Zeit. Phys. Chem.*, 1927, 130, 346.

with the concentration of alkali On the basis of Ostwald's valency rule, Pauli[1] has estimated from conductivity experiments that casein forms a tervalent and globulin a tetravalent anion

For ampholytes,[2] it may be shown practically, as well as theoretically, that there is a definite concentration of hydrogen ion at which the number of anions becomes equal to the number of cations This is known as the *isoelectric point* Under the influence of an electric field the numerical equivalence of anions and cations is indicated by symmetrical movement to anode and cathode Since, however, the number of ions is at a minimum at the isoelectric point (see below) the electrical migration is also at a minimum Each protein has its own characteristic isoelectric point, corresponding, in the cases so far examined, to very faintly acidic solutions

At the isoelectric point the sum of the ions reaches a minimum as compared to the number of undissociated molecules Hence, if either strong alkali or acid is added in very small concentrations to a protein solution at the isoelectric point, the dissociation is increased owing to salt formation

The faintly acid solution at the isoelectric point represents the optimum condition for the heat coagulation of a large number of proteins (Michaelis) At this point serum globulin is precipitated, even without heating

It has been suggested by Hardy and Bredig that agglomeration is hindered by the electric charge on the colloid particles, but is promoted by surface tension At the isoelectric point the charge is at a minimum, and the surface tension therefore gains the upper hand

Viewed from another standpoint, the excess of undissociated protein molecules present at the isoelectric point also has an influence on precipitation According to Pauli, the ions of a protein differ from the undissociated molecules in their behaviour, they are heavily hydrated, *i e*, they are combined with molecules of water, which they lose when they pass back into undissociated molecules It is very probable that this process is directly concerned in solubility changes The strong hydration of protein ions, as compared with neutral molecules, is confirmed by the fact that the increased dissociation resulting from the addition of acids or alkalis to a protein solution is accompanied by a marked increase in viscosity Consequently, at the isoelectric point the number of hydrated ions and the inner friction of the solution are both at a minimum

In a similar way, other physical properties of protein solutions are dependent on the state of ionisation For example, ionised protein is more strongly laevorotatory than neutral protein

[1] Pauli, *Biochem Zeitsch*, 1922, **127**, 150, see, however, L van Slyke and A Bosworth, *Journ Biol Chem*, 1913, **14**, 211, 227 [2] An ampholyte is an amphoteric electrolyte, that is, one which dissociates both as an acid and as a base

All these facts indicate that the electrical condition of the protein particles, unlike that of other colloids, can be largely explained on the basis of the dissociation theory. No distinct boundary line can therefore be drawn between solutions of crystalloid electrolytes and protein solutions, and the reactions of proteins are thus to a large extent true chemical reactions.

The presence of proteins in a solution modifies the properties of other dissolved substances, owing to adsorption, hydration, etc. In some cases proteins prevent the deposition of difficultly soluble salts from solution. This fact is of great biological importance and accounts for the existence of dissolved calcium salts in the body fluids. On the other hand, the presence of proteins lowers the solubility of many easily soluble salts. Proteins are also efficient protective colloids; in minute amounts they protect suspensoids from precipitation by electrolytes. The number of milligrammes of a protein, which is just insufficient to protect 10 c.c. of a standard colloidal gold solution from precipitation by 1 c.c. of a 10 per cent. solution of sodium chloride, is known as the *gold number* of the protein concerned (Zsigmondy[1]). This number is characteristic for each individual protein.

Crystallisation of Proteins.—The inability of proteins to diffuse through membranes is in strong contrast to the ease of diffusion of crystalloids, and led at first to the conclusion that proteins could not be obtained in a crystalline condition. This was later proved to be incorrect. On the one hand, protein crystals have been found as such in nature, as in the aleurone grains which are widely distributed in the seeds of plants; and, on the other hand, a number of proteins which do not naturally occur in the crystalline state have been converted into this form. For example, crystalline egg albumin was obtained by Hofmeister,[2] and horse serum albumin, hæmoglobin, and globulins from plant seeds have also been prepared in the crystalline condition.

From the work of Sorensen,[3] it appears that the crystallisation of proteins in no way differs from that of crystalloids. But, despite this similarity, it is not possible by recrystallisation to purify them to the same extent as other organic compounds, owing to their sponge-like capacity for absorbing impurities from solution.[4]

Although various proteins have been found in the crystalline state in animals and plants, or have been converted into the crystalline form by artificial means, none of these compounds can be regarded as chemically pure. In all probability no protein has yet been obtained in a homogeneous condition.

For this reason, some degree of uncertainty is attached to all

[1] F. N. Schulz and Zsigmondy, Hofmeister Beiträge, 1902, 3, 137. [2] F. Hofmeister, *Z. physiol. Ch.*, 1889, 14, 165; 1891, 16, 187. [3] Sörensen and M. Höyrup, *Z. physiol. Ch.*, 1918, 103, 15. [4] Compare Wichmann, *Z. physiol. Ch.*, 1897, 27, 581; see also Kossel, *Ber.*, 1901, 34, 3229, 3231.

investigations so far carried out in protein chemistry, and more especially to molecular weight determinations.[1]

Molecular Weight Determinations.—Among the usual physico-chemical methods employed for the *estimation of molecular weights*, the ebullioscopic method cannot be used owing to the changes undergone by proteins under the influence of heat. The values hitherto obtained by the cryoscopic method are remarkably small,[2] *e.g.* for silk fibroin about 350, a phenomenon for which no satisfactory explanation has yet been advanced.

Sorensen,[3] as a result of careful direct *osmotic pressure measurements*, estimates the molecular weight of crystalline egg albumin at 34,000, and Pauli,[4] from determinations of the valency of the ions of casein and globulin, has calculated that these two proteins have molecular weights of about 3000 and 12,000 respectively.

Minimum values for the molecular weights of various proteins have been calculated from their *sulphur content*, as determined by elementary analysis. By simple computation it is easily shown that for a sulphur content of 1 per cent. the molecular weight of the protein must be at least 3200. The following figures may be taken as examples of such estimations:

	Per cent. of S	Mol. wt. (assuming 1 atom S to each mol. protein)
Edestin (crystallised)	0.87	3680
Oxyhæmoglobin (horse)	0.43	7440
Egg albumin (crystallised)	1.3	2460

In this manner it is possible to determine the smallest molecular weight which will satisfy the analysis figures. The value so obtained, however, is an empirical one, and the actual molecular weight may be a multiple of it. Schulz has estimated the molecular weights of edestin, oxyhæmoglobin, and egg albumin, to be 7300, 14,800, and 4900 respectively.

The molecular weight of oxyhæmoglobin may also be calculated in an analogous manner from its *iron content*. As has already been stated, this substance is a compound of a simple protein (*globin*), containing sulphur, and a pigment (*hæmatin*) in which iron is present (p. 571). Although it has not yet been proved experimentally, it is probable that each oxyhæmoglobin molecule consists of one molecule of globin and one molecule of hæmatin. On this assumption the sulphur content of oxyhæmoglobin (0.43 to 0.67 per cent.) corresponds to a molecular weight of 14,800 to 9500, whilst the iron content (0.4 to 0.5 per cent.) corresponds to 14,000 to 11,200.

Molecular weights have also been calculated from the proportion of metal contained in the precipitates which are formed by adding

[1] F. N. Schulz, *Die Grosse des Eiweissmoleculs*, Jena, 1903. [2] R. O. Herzog and M. Kobel, *Z. physiol. Chem.*, 1924, **134**, 296. [3] Sorensen and Höyrup, *Z. physiol. Ch.*, 1918, **106**, 1. [4] W. Pauli, *Biochem. Zeitsch.*, 1922, **127**, 150.

salts of heavy metals (*e g*, copper sulphate) to protein solutions[1] This cannot be discussed in detail here

Svedberg has developed an *ultracentrifuge method* of determining molecular weights He concludes that a number of proteins are *monodisperse* (homogeneous with regard to molecular weight) when examined in the neighbourhood of the isoelectric point, and divides them into two groups namely, those giving values of the order of millions, *e g* the hæmocyanins, and others the molecular weight of which is either 34,500 or this figure multiplied by 2, 3 or 6 (ovalbumin, 34,500, hæmoglobin, 68,000, serum albumin, 67,500, serum globulin, 103,800, edestin, 208,000) At higher and lower p_H values the protein molecule appears to break down, although in many cases this change is reversible[2]

From these examples it will be seen that no exact estimation of the magnitude of the protein molecule can yet be made It remains for physical chemistry to discover a satisfactory solution of the problem

Composition of Proteins—The pure chemistry of the proteins is based on that of the amino acids, which have already been dealt with on pp 210 to 225 Some special characteristics of the proteins are discussed in the following pages

Proteins in general contain the five elements, carbon, hydrogen, oxygen, nitrogen, and sulphur[3] The percentage of each of these present varies for different types within the following limits

Carbon	50 5	to	54 6	per cent
Hydrogen	6 5	„	7 3	„
Oxygen	21 5	„	23 5	„
Nitrogen	15 0	„	17 6	„
Sulphur	0 5	„	2 2	„
Phosphorus	0 42	„	0 85	„

The two other main groups of foodstuffs, fats and carbohydrates, differ from proteins in containing no nitrogen In physiology, therefore, the quantity of nitrogen utilised by the organism gives a direct measure of the amount of protein metabolism

The nitrogen in proteins occurs in various states of combination Most of it is present in *peptide groups* derived from monamino acids and after hydrolysis of the protein the resulting free amino groups can be estimated by means of nitrous acid (van Slyke)[4]

The *basic nitrogen* is derived from the free amino groups contained in basic proteins, which are precipitated by phosphotungstic acid The majority of these compounds are built up from molecules of diamino

[1] J Harnack, "Untersuchungen über die Kupferverbindungen des Albumins," *Z physiol Ch*, 1881, 5, 198 Schulz and Zsigmondy, *loc cit* [2] The Svedberg, *Trans Farad Soc*, 1930, 26, 740 [3] The nucleins, to be described later, contain phosphorus Iron is present in hæmoglobin and copper in hæmocyanin In addition, traces of iron are generally found in the ash of proteins [4] D D van Slyke, *Ber*, 1910, 43, 3170, 1911, 44, 1684

acids in such a way that only one of the two amino groups takes part in peptide union, the other remaining free. Nitrogen present in the latter state can be estimated by formol titration (Sorensen), or by means of nitrous acid (see above).

The *guanidine nitrogen* of basic proteins is contained in the free guanidine group of arginine.

Finally, it is possible that nitrogen may also be present in an *acid amide grouping*, such as is found in the half amides asparagine and glutamine (pp. 282, 283). The occurrence of the half amides of aspartic and glutamic acids in the protein molecule is strongly supported by the work of Osborne, Thierfelder[1] and others. Nitrogen in acid amide groups can be removed as ammonia by treating the protein with dilute mineral acids.

Some nitrogen may also occur in the form of *diketopiperazine groups*.

Owing to the formation of undefined by-products during hydrolysis these different nitrogen fractions cannot be estimated accurately.

The sulphur in proteins is derived from cystine, cysteine (thioserine), and a third component which has been identified by Barger as γ-methylthiol-α-aminobutyric acid (*methionine*, see p. 234).

The instability of the protein molecule has rendered the investigation of the structure of these compounds a very difficult problem to attack by any method other than hydrolysis. Nevertheless, in recent years proteins have been acetylated and methylated, and the products reduced and subsequently hydrolysed, with a view to gaining information as to their constitution.[2] Proteins have also been halogenated.

Halogens[3] enter into the ring systems of cyclic amino acids, and change the protein in such a way that sulphur can no longer be removed from it by treatment with alkalis. For a given method of halogenation, the amount of halogen taken up by a particular kind of protein is constant.

Kossel and Edlbacher[4] have methylated proteins, chiefly protamines, by means of dimethyl sulphate. The N-methyl number, *i.e.*, the number of *N methyl groups* corresponding to 100 atoms of nitrogen, was found to be a characteristic for each individual protein examined. It was shown that very similar compounds may give quite different N-methyl numbers.

Reactions of Proteins

No single one of the following reactions is in itself a reliable test for the presence or absence of proteins, but cases of doubt can be determined by the use of several of them.

The reactions of proteins are divided into precipitation and colour

[1] Thierfelder and v. Cramm, *Z. physiol. Ch.*, 1918, **105**, 58. [2] Troensegaard, *Z. physiol. Ch.*, 1923, **127**, 84, 137. [3] See Cohnheim, *Chemie der Eiweisskörper* (Brunswick, 1911); see also Siegfried and Reppin, *Z. physiol. Ch.*, 1915, **95**, 18. [4] *Z. physiol. Ch.*, 1918, **107**, 52.

reactions For determining the presence of proteins in animal fluids, certain precipitation reactions only may be employed Whereas the colour reactions depend on the occurrence of certain chemical groups in the protein molecule, and are therefore given also by the corresponding non-protein hydrolytic products, the precipitation reactions are due to the colloid nature of the protein and these alone give reliable information as to the presence of protein as such Precipitation reactions are accordingly employed in medical science for the detection of protein matter in animal fluids (*e g* urine) Colour reactions should be applied exclusively to pure protein solutions

Precipitation Reactions 1 *Coagulation Test*—Proteins are precipitated when heated in faintly acid solution, especially in the presence of neutral salts (see p 756)

2 *Heller's Test*—Proteins are coagulated by treatment with concentrated acid, *e g* nitric acid This test is carried out as follows — Concentrated nitric acid is gently poured down the side of the test-tube containing the protein solution The acid forms a lower layer and a white disc of precipitated protein appears at the junction of the two liquids

3 Proteins are precipitated by the addition of small quantities of *salts of heavy metals*, such as ferric chloride, ferric acetate, copper sulphate, copper acetate, mercuric chloride, and basic lead acetate

4 Owing to their character as weak bases, proteins are precipitated by the *alkaloid reagents*, *e g* phosphotungstic acid and phosphomolybdic acid (in the presence of mineral acid), tannin, hydroferrocyanic acid, and picric acid As phosphotungstic acid brings about complete precipitation, it is frequently employed for the removal of dissolved protein, more especially of basic protein The reactions with tannin and hydroferrocyanic acid are also very sensitive The latter is usually carried out by treating the protein solution with potassium ferrocyanide and acetic acid Potassium mercuric iodide, like trichloroacetic acid, is often used to remove proteins from physiological solutions Protein in urine is detected by reactions 1 and 2, and by precipitation with hydroferrocyanic acid, more recently a 20 per cent solution of sulphosalicylic acid has been introduced for this purpose The precipitation reagents are used in histology as fixatives

Colour Reactions 1 *Biuret Reaction*—This has been described on p 224 It is chiefly used for distinguishing between proteins and their partially hydrolysed products, as peptones and albumoses give a redder tint than the proteins The biuret reaction, however, is not a reliable test for a protein, since it is also given by certain other substances.[1]

2 *Millon's Test*—On boiling protein, either in the dissolved state or in solid form, with an aqueous solution of nitrous acid in mercuric nitrate, the coagulated protein and the liquid are coloured pink to

[1] H Schiff, *Ber*, 1896, **29**, 298, 1897, **30**, 2455

dark red This reaction is given by all compounds having phenolic groups in the molecule, and in the case of protein is due to the presence of tyrosine residues

3 *Xantho protein Reaction*—On treating a protein solution with strong nitric acid, a yellow coloration is produced, occasionally in the cold, but usually only after heating On addition of excess of sodium hydroxide the liquid becomes reddish brown, whereas with excess of ammonia it turns an orange colour This reaction depends on the presence of tyrosine and tryptophane groups, but is not peculiar to proteins

4 The *Adamkiewicz-Hopkins Reaction*—With a mixture of concentrated sulphuric acid and glyoxalic acid (or a solution of glyoxalic acid in glacial acetic acid) proteins give a reddish violet coloration, slowly in the cold but more rapidly on warming This reaction is due to the presence of tryptophane groups and hence is not given by gelatin, in which this group is absent

5 The *Ninhydrin Reaction*[1] of Abderhalden and Schmidt When heated with triketo-hydrindine hydrate (ninhydrin), proteins and all α-amino acids give a blue coloration

6 The *Lead Sulphide Test*—When a protein solution is heated with an alkaline solution of a lead salt, *e g* lead acetate, a black precipitate or a dark brown coloration is produced, owing to the formation of lead sulphide

7 The *Iodine Test*—For microscopic detection, proteins are mixed with tincture of iodine or a solution of iodine in potassium iodide The coagulum develops a yellow colour

Classification of the Proteins and the Characteristics of the Individual Groups

As yet it is not possible to classify the proteins on a purely chemical basis, although they could perhaps be grouped in accordance with the relative proportions of mono- and diamino-acids formed from them on hydrolysis A better method is to base the classification on physico chemical differences In this way the proteins can be divided into two main groups and a number of sub-groups

(a) *Simple Proteins*

I True proteins

(*a*) Albumins (serum albumin, ovalbumin, lactalbumin), (*b*) globulins (serum globulin, ovoglobulin, lactoglobulin, cytoglobulin), (*c*) plant globulins and plant vitellins, (*d*) fibrinogen, (*e*) myosin, (*f*) phospho-proteins, which contain phosphorus (caseinogen, vitellins), (*g*) histones, and (*h*) protamines

[1] *Cf* Abderhalden and H Schmidt, *Z physiol Ch*, 1913, 85, 143 Halle, Löwenstein, and Pribram, *Biochem Zeitsch*, 1913, 55, 357

II Albuminoids[1]

(*a*) Collagen, (*b*) keratin (from hair, feathers, horn, etc), (*c*) elastin, (*d*) fibroin (from silk), (*e*) spongin, conchiolin, (*f*) amyloid, (*g*) albumoid and melanins

(b) *Conjugated Proteins*

Compounds of proteins with other and usually highly complex substances

(*a*) Nucleoproteins compounds of proteins with nucleic acids, (*b*) chromoproteins (hæmoglobins), (*c*) glucoproteins compounds containing carbohydrates (mucins)

Only a short account of the different groups can be given here

I—SIMPLE PROTEINS

I *True Proteins*

The **albumins** form a well-defined and readily accessible group of proteins, and, as already stated, may be obtained in a crystalline condition[2] They are soluble in pure water, in dilute salt solutions, and in acids and alkalis Pure solutions of albumins are neutral They are not precipitated from these solutions by saturation with salt or magnesium sulphate, nor by half saturation with ammonium sulphate In this last respect they differ from the globulins, which are frequently associated with them in nature On the other hand, the albumins are completely precipitated when their solutions are saturated with ammonium sulphate On treatment with caustic soda, ovalbumin gives *egg protalbinic acid* and *egg-lysalbinic acid*[3] The albumins so far investigated contain a large percentage of sulphur and yield no glycine on hydrolysis

The **globulins** differ in a number of ways from the albumins For example, they do not dissolve in pure water, although they are soluble in dilute solutions of neutral salts and of alkali carbonates They behave as acids and are precipitated by carbon dioxide from very weakly alkaline solutions, an excess of carbon dioxide, however, is to be avoided They are very easily denatured, and may be precipitated from their solutions by dilution with water or by acidification Globulins are completely salted out with magnesium sulphate at 30°, but with sodium chloride the precipitation is incomplete They are precipitated when their solutions are half saturated with ammonium sulphate, a property which is used in the separation of globulins from

[1] These are frequently grouped under the heading of unclassified proteins or *scleroproteins* They differ from the "true proteins" chiefly in their physical properties, *e g* insolubility, and in their failure to give certain of the typical protein reactions, but no sharp distinction can be drawn between the two groups [2] For the distillation of ovalbumin under diminished pressure, see A Pictet and M Cramer, *Helv Chim Acta*, 1919, 2, 188 [3] Skraup and Hummelberger, *Monats*, 1909, 30, 125

albumins This is the most pronounced difference to be observed between the two classes

The **plant globulins**, which function as reserve material in the seed, are also very readily isolated The best known of these is **edestin**, which is soluble at 60° in a 3 per cent solution of sodium chloride, from which it may be obtained in a crystalline state On partial hydrolysis with caustic soda edestin yields three products a protalbinic acid which is very sparingly soluble in water, an albumose (lysalbinic acid) which is soluble in water and can be precipitated with ammonium sulphate, and a peptone which cannot be salted out [1]

From plant seeds such as barley and wheat, Osborne and his collaborators have isolated *prolamines*, or *gliadins*, a class of protein of which no representatives have yet been discovered in the animal kingdom Unlike other proteins they are soluble in 75 per cent alcohol, and contain a large proportion of glutamic acid (up to 40 per cent)

Myosin, present in muscle, possesses the properties of the globulins, and plays an important part in the phenomenon known as *rigor mortis*

Fibrinogen and *caseinogen* are distinguished by their property of clotting under the influence of certain ferments This process is not to be confused with coagulation The clotted substances are insoluble in water and salt solutions, and can be coagulated by heating or by treatment with alcohol **Fibrinogen** is a protein contained in the blood of all vertebrates In the presence of calcium salts and under the influence of a ferment, thrombase, it is converted into **fibrin**, the clotting of blood is due to this change

The **phosphoproteins** contain phosphorus At one time they were known as nucleo-albumins and were grouped with the nucleoproteins Unlike the latter, however, they are not found in combination with nucleic acid Phosphoproteins are distinctly acid in character, and colour litmus red They are insoluble in water, but readily dissolve in the form of their alkali and ammonium salts From these solutions the addition of acids precipitates the original compounds The salts are not coagulated on being heated in solution This group includes *caseinogen* and *vitellin*, which is present in egg yolk

Caseinogen [2] is the characteristic protein of milk, in which lactalbumin and lactoglobulin are also present As yet it has not been definitely ascertained whether the milk of different animals contains one and the same caseinogen The compound is present in milk in the form of the soluble calcium caseinogenate On addition of acid, caseinogen is precipitated owing to its insolubility in water Hence it may be purified by solution in alkali and reprecipitation with acid Under the influence of rennin, a ferment

[1] Skraup and Wöber, *Monats*, 1909, 30, 289 [2] R Scherer, *Das Casein Dessen Zusammensetzung, Eigenschaften, Herstellung und Verwertung* Second Edition, Vienna, 1919

secreted by the mucous membrane of the stomach, caseinogen is converted into *casein*[1] The latter differs from caseinogen in the insolubility of its calcium salt Consequently, if calcium salts are already present in the solution in which this change occurs, as is the case in milk, insoluble calcium caseinate or curd separates out The conversion of milk into junket by means of extract of rennet is therefore a dual process, involving the production of casein from caseinogen and the precipitation of insoluble calcium caseinate The action of rennin is assisted by the presence of small amounts of acids, and is retarded by alkalis In the preparation of cheese the curd is fermented by more prolonged treatment The artificial milk preparation, *eucasein*, is the ammonium salt of caseinogen, *nutrose* and *plasmon* are sodium salts

The souring of milk in summer, *i e*, acid clotting, is to be distinguished from the curding produced by rennin The former is a direct result of the fermentation of the lactose by micro-organisms, leading to the formation of lactic acid which precipitates the caseinogen (see above) This process can therefore be delayed by the addition of sodium bicarbonate The residual clear liquid is known as sour whey

On the other hand, the residual liquid from cheese is known as sweet whey, owing to the absence of acid

Numerous analyses have been made of caseinogen from cow's milk, the most reliable of which are probably the following due to Hammarsten —C 52 96 per cent, H 7 05 per cent, N 15 65 per cent, S 0 758 per cent, P 0 847 per cent In this connection, however, it must be remembered that caseinogen has not yet been obtained in the crystalline state On hydrolysis with sulphuric or hydrochloric acid caseinogen yields a number of products, including *glutamic acid*[2] and three different compounds of the composition of *leucyl valine anhydride*, $C_{11}H_{20}O_2N_2$

In addition to its use in the preparation of patent foods such as plasmon, sanatogen, etc, caseinogen is employed in large quantities in the manufacture of artificial bone and ivory goods, and electrical insulating material

The last two groups of simple proteins, viz, the *histones* and *protamines*, contain a large proportion of diamino acids and are basic in reaction They appear to be of relatively simple structure

Histones always occur in nature in combination with other compounds, as in the spermatozoa of fish Globin, the protein component of the red colouring matter of blood, also belongs to this group Histones have a pronounced basic character and are soluble in acids[3] From aqueous solutions they are precipitated by addition of ammonia,

[1] Part of this undergoes a further decomposition, E Petry, *C*, 1906, II, 803 [2] Skraup and Lihk, *Monats*, 1909, 30, 287 [3] See J Bang, *Z physiol Ch*, 1897, 27, 463, 1900, 30, 508

but redissolve in excess of the reagent They are not coagulated by boiling, except in the presence of salts It is not at present possible to give a clear definition of a histone, but these compounds appear to occupy an intermediate position between the protamines and other proteins (Kossel)

Protamines have hitherto been found only in combination with nucleic acids in the spermatozoa of fish The individual protamines are named after the fish from whose testicles they are obtained, *e g* *salmine* from salmon, *sturine* from sturgeon, and *clupeine* from herring They have been investigated more particularly by Kossel[1] A quantitative examination of the products obtained by hydrolysing protamines by means of acids or trypsin has shown that they contain approximately $\frac{8}{9}$ of their nitrogen in the form of arginine, together with small quantities of monamino acids The formula of salmine is possibly $(C_{81}H_{155}N_{15}O_{18})_x$ or $(C_{98}H_{186}N_{54}O_{21})_x$, in which x may be 1 or greater than 1 The protamines are strong bases but very little is known as to their properties in the free state. The best known salts are the sulphates, which can be purified by precipitation with alcohol from sulphuric acid solution The hydrochlorides are more readily soluble than the sulphates Solutions of the salts are laevorotatory The platinum double salts of the protamines are either insoluble or sparingly soluble in water, and have been frequently used for analysis The compound of this type formed by salmine approximates in composition to $2(C_{81}H_{155}N_{15}O_{18}), 23HCl, 11\ PtCl_4$

Protamines cannot be coagulated by heat, but may be salted out by use of ammonium sulphate or sodium chloride For their methylation, see p 762

2 *Albuminoids*

The albuminoids are only found in animal bodies, in which they are present in the undissolved state They constitute the framework of animal tissue, and play the same part in the animal body as certain carbohydrates (*e g* cellulose) do in the vegetable kingdom They cannot be dissolved without undergoing chemical change, and differ from other proteins chiefly in their resistance towards chemical reagents As already mentioned, there are different kinds of albuminoids

Collagen is the most widely distributed of these compounds It forms the basis of bone and cartilage, and is the chief constituent of the connective tissues When boiled with water collagen passes more or less readily into solution, hydrolytic decomposition probably taking place during this process The soluble product is known as **gelatin** (*glutin*) On being cooled to room temperature the solution

[1] Kossel has given a summary of his results in "Ueber die einfachen Eiweisskörper," *Biochem Centralblatt*, 1906, V For sturine, see Kossel and Weiss, *Zeit f physiol Ch*, 1912, 78, 402

sets to a jelly, which again liquefies on warming. Gelatin is not thrown out of solution by nitric or other mineral acid, but is precipitated by mercuric chloride in the presence of hydrochloric acid, and also by tannin.

The collagens obtained from different organs and different animals are not necessarily identical. Collagen differs from the "true proteins" more especially in its high content of nitrogen (17.9 per cent). On hydrolysis it yields, in addition to other products, an exceptionally high proportion of glycine (15 to 18 per cent). On the other hand, collagen contains neither tryptophane nor tyrosine residues, and the protein reactions due to the presence of these amino acids are therefore not given by it.

Keratin is contained in most of the horny structures produced by the epidermal cells of the skin, *i.e.* horns, hoofs, nails, feathers and hair. It is insoluble in water, dilute acids and alkalis, but when boiled with alkalis or heated under pressure with water it undergoes decomposition and passes into solution. Keratin contains a very high proportion of sulphur (4 to 5 per cent), the greater part of which can be removed in the form of hydrogen sulphide by boiling with alkali, or even with water. According to Drechsel, another substance belonging to this group is **gorgonin**, the insoluble protein in coral. Similarly **iodospongin**, the skeletal tissue of the tropical horn sponge, is probably to be classified with the keratins. It was shown by Morner that gorgonin, iodospongin, and other proteins of the skeletal tissue of anthozoa all contain halogens. From the hydrolysis products of these compounds have been isolated 3 5-*diiodo-tyrosine* (*iodo-gorgonic acid*), and 3 5 *dibromo-tyrosine* (*bromo gorgonic acid*).

Elastin forms the elastic fibres of animal connective tissue, and is generally prepared from the cervical ligament of the ox. Like keratin, it is insoluble in dilute acids and alkalis, but contains a comparatively high carbon and low sulphur content. When elastin is warmed with dilute alkalis the sulphur is completely removed.

Fibrosin or silk fibroin is the chief constituent (about 53 per cent) of silk, and has been more fully investigated than any other albuminoid. When silk is boiled for several hours with water, *silk gelatin* or **sericin** passes into solution, leaving behind the insoluble silk fibroin. The latter is insoluble in dilute but soluble in concentrated acids and alkalis. It is precipitated from its solutions on neutralisation, or addition of alcohol. By partial hydrolysis of fibrosin Abderhalden[1] obtained d-*alanyl-glycine*, and d-*alanyl-glycyl* l-*tyrosine*. The latter, which has also been prepared synthetically, was the first tripeptide to be obtained by the partial hydrolysis of a protein.

Spongin is the chief constituent of the common sponge, and

[1] Abderhalden, *Z physiol Ch*, 1911, **72**, 1

resembles keratin in many respects At ordinary temperatures it only dissolves in very concentrated sulphuric or hydrochloric acid, but it is more readily soluble in alkali *Conchiolin* is the organic component of the shells of the mussel and snail, *cornein* is the corresponding constituent of coral

Amyloid takes its name from the fact that under certain conditions it yields a blue coloration with iodine (*cf* starch, amylum) It does not occur normally in the body but is produced under pathological conditions Whereas healthy tissue is coloured blue with methyl violet, tissue containing amyloid is coloured ruby-red

In the group of albuminoids are included a large number of other proteins, of which so little is known that they cannot be discussed here

II —CONJUGATED PROTEINS

As has already been stated, the conjugated proteins are compounds of proteins with other complex substances, the non-protein part of the molecule being known as the *prosthetic group*

Nucleoproteins are compounds of proteins with nucleic acids, and are so named because they are the chief constituents of the cell nucleus in plant and animal organisms They are all soluble in water and salt solutions, and dissolve with special ease in alkalis They are strongly acid in character, may be salted out from their solutions, and are denatured by heat Nucleoproteins are present in all cell nuclei and have been prepared from a number of very different organs, including the spermatozoa of fish Careful investigations have been carried out on yeast nucleoprotein, the nucleic acid of which is readily isolated

The manner in which the nucleoproteins are built up from the two components, protein and nucleic acid, is still uncertain It appears, however, that the nucleic acid is combined with two parts of protein, one of which is easily detached, leaving a compound still containing nucleic acid united with protein The latter substance is known as a *nuclein* On further treatment the nuclein breaks down to give a nucleic acid

The constitution of the **nucleic acids**[1] has been examined by Feulgen, Kossel, Levene, Osborne, Steudel, and others According to the method of treatment these acids may undergo partial or complete hydrolysis

Complete hydrolysis with dilute mineral acids results in the formation of *phosphoric acid*, *purine* and *pyrimidine bases*, and a *carbohydrate* Among the purine bases have been found xanthine, hypoxanthine, adenine and guanine, and among the pyrimidine

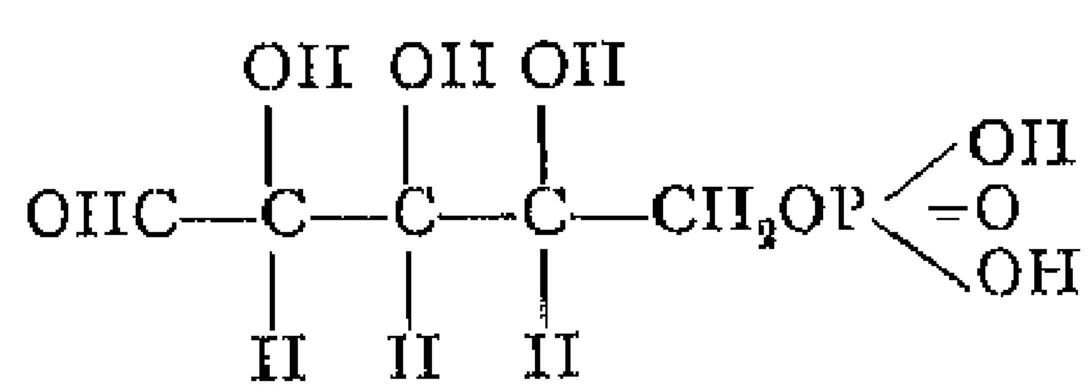
[1] See also *Nucleic Acids*, by W Jones (Longmans, Green) *Nitrogenous Constituents of the Living Cell*, Plimmer *Die Nucleine*, Feulgen (J Springer, Berlin, 1924)

bases cytosine, uracil and thymine. The actual products obtained vary with the type of acid hydrolysed. The carbohydrate present in the vegetable and certain of the animal nucleic acids, *e.g.* yeast nucleic acid, has been identified as the pentose d-*ribose* (see p. 296). In many animal nucleic acids the place of ribose appears to be taken by another carbohydrate, the constitution of which has not been definitely established.

According to a recent investigation of Levene,[1] however, the pure sugar has been isolated from thymonucleic acid by employing a very mild hydrolytic agent (intestinal juice) and has been identified as a *desoxypentose*. If this is confirmed, it is clear that a hitherto unsuspected significance must be attached to pentoses in relation to animal metabolism.

By the hydrolysis of nucleic acids with ammonia, Levene[2] has obtained *mono-nucleotides*. These are compounds built up of a molecular proportion of carbohydrate united with one of phosphoric acid and one of base.

The problem of determining the manner in which these component parts are linked together in the mono-nucleotides has also been partially solved by the use of hydrolytic methods. For example, if the nucleotide *inosinic acid*, obtained from muscle, is heated with 1 per cent hydrochloric acid, it yields *ribose-phosphoric acid*,[3] which by oxidation with nitric acid has been shown to contain the phosphoric acid united to carbon atom 5. Ribose-phosphoric acid may therefore be represented as



When nucleic acids are heated under pressure in ammoniacal or neutral solution, the nucleotides first formed part with phosphoric acid and yield *nucleosides*,[4] which are crystalline compounds of carbohydrate and base. The union between carbohydrate and base in these compounds is glucosidic in type, *i.e.*, at the aldehydic carbon atom of ribose. It is still a matter of controversy which carbon atom of the base is concerned in this union; in the purine bases it is either atom 7 or 8.

Newer investigations indicate that in other nucleotides the phosphoric acid group may be linked to different carbon atoms of the ribose molecule. Thus Embden and Zimmermann[5] have shown that

[1] Levene and London, *J. Biol. Chem.*, 1929, **81**, 711. See also Feulgen, *Z. physiol. Ch.*, 1917, **100**, 241. [2] P. A. Levene, *J. Biol. Ch.*, 1919, **40**, 415; 1920, **41**, 19. [3] Levene and Jacobs, *Ber.*, 1911, **44**, 746. [4] Levene and Jacobs, *Ber.*, 1909, **42**, 2469, 2703. [5] *Zeitschr. für physiol. Chem.*, 1929, **181**, 130.

adenylic acid from muscle is not identical with the adenylic acid from yeast As each compound, after removal of base and phosphoric acid, yields the same hypoxanthine-riboside, the difference between the two nucleotides can only lie in the different point of union of the phosphoric grouping

The nucleotides have therefore the following structure

phosphoric acid—carbohydrate—base

Carbohydrates form more stable compounds with pyrimidine than with purine bases

Nucleic acids are composed of several (generally four) nucleotide molecules, which are probably linked together through the phosphoric acid groups They are therefore to be regarded as polynucleotides Hammarsten classifies these compounds as follows

1 *Simple Nucleic Acids or Nucleotides*—Included in this group is *inosinic acid*, which was isolated by Liebig[1] from meat Inosinic acid is a laevorotatory syrup of the structure

phosphoric acid—*d*-ribose—hypoxanthine

It forms crystalline salts, the barium compound being sparingly soluble *Guanylic acid*, of the composition

phosphoric acid—*d*-ribose—guanine,

was first prepared from the pancreas by Bang It yields crystalline salts, and has itself been prepared in the crystalline condition from yeast nucleic acid by Levene It is a constituent of other nucleic acids, but also occurs in the free state in the pancreas and other organs

2 The true *compound nucleic acids* or *polynucleotides* are divided into two groups, viz, *thymus nucleic acids*, obtained from animal organs, particularly the thymus gland, and *plant nucleic acids* Up to the present, polynucleotides have only been obtained as amorphous dextrorotatory substances They are sparingly soluble in water, practically insoluble in alcohol and ether, but soluble in ammonia and alkalis They are precipitated from solutions of their salts by the addition of hydrochloric acid The salts can be precipitated by means of certain dye bases, and owing to the solubility of the product in alcohol this method is recommended by Feulgen for their purification *Yeast nucleic acid*, which is probably identical with the *tritico-nucleic acid* isolated from wheat embryo, is composed of four nucleotide molecules, containing *d* ribose as carbohydrate and guanine, adenine, cytosine, and uracil as bases

Hæmoglobins—These are compounds of proteins with pigments containing iron *Hæmoglobin*, the red colouring matter of the blood

[1] Liebig, *Ann*, 1847, 62, 317, Haiser and Wenzel, *Monats*, 1908, 29, 161

of vertebrates, is the chief constituent of red blood corpuscles It is built up from a protein, *globin*, and a prosthetic compound, *hæmatin* Hæmatin contains iron, and has already been described in detail on p 571, *et seq* It is probable that the blood of different animals contains different hæmoglobins With oxygen, carbon monoxide, and other gases, hæmoglobin combines to give loose addition compounds, such as oxyhæmoglobin and carboxy-hæmoglobin The most important of these is oxyhæmoglobin, which contains one molecule of hæmoglobin to one of oxygen It readily gives up its oxygen again[1] and thus plays an essential part in the respiration of the vertebrates This compound is often loosely termed hæmoglobin Since it crystallises better than the true hæmoglobin, and is readily formed from the latter in the presence of atmospheric oxygen, oxyhæmoglobin has been largely used in analyses and other investigations on the colouring matter of blood Owing to the extremely high molecular weight of these compounds, there is very little difference between the percentage composition of hæmoglobin and oxyhæmoglobin Hæmoglobins from different kinds of animals differ considerably in their solubility in water Hæmoglobin is not salted out from a neutral solution by the addition of sodium chloride or magnesium sulphate, but only by saturation with a mixture of magnesium and sodium sulphates

Under the influence of acids hæmoglobin decomposes into globin and hæmatin With hydrochloric acid, for example, it yields globin and an ester-type of compound of hæmatin and hydrochloric acid, known as *hæmin* The latter has already been described on p 571, but it may be added that its property of separating in characteristic reddish-brown microcrystalline needles is of importance for the detection of blood stains in forensic medicine[2]

The compound formed by union of hæmoglobin with carbon monoxide is more stable than oxyhæmoglobin, and the poisonous character of carbon monoxide is due to the ease with which it displaces oxygen from oxyhæmoglobin, thus preventing oxygen from being carried to the tissues

Glucoproteins are compounds of proteins with carbohydrates As might be expected, their nitrogen content (11 7 to 12 3 per cent) is less than that of the true proteins The group consists essentially of the *mucins*, present in the mucous membranes, together with the related compounds, pseudo-mucins, mucoids and chondroproteins It has already been stated on p 304 that ordinary mucins yield *glucosamine*

[1] In addition to the unstable oxyhæmoglobin, a stable compound of hæmoglobin with oxygen is known as **met-hæmoglobin** This is formed from oxyhæmoglobin when the latter is kept for some time, or from hæmoglobin by the action of various reagents It is apparently related to hæmoglobin as a ferric to a ferrous compound (Conant and Fieser, *J Biol Chem*, 1925, 62, 595)

[2] For procedure, see A Lucas, *Forensic Chemistry*, p 25 (Arnold, 1921)

on hydrolysis, in a similar manner the mucin from frog spawn yields *galactosamine* The *chondroproteins* contain chondrosamine, a sugar of a different configuration, which appears to be closely related to galactosamine[1]

The *mucins* are widely distributed in nature and are known to be constituents of mucus and saliva They are markedly acid in character, do not dissolve in pure water, but dissolve readily in alkali carbonates and ammonia From these solutions they are precipitated by the addition of excess of acetic acid They are not coagulable by heat The mucins are very closely related to the chondroproteins Of the latter, the most carefully investigated representative is *chondromucoid*, which with collagen is one of the chief constituents of cartilage On hydrolysis it yields protein and *chondroitin sulphuric acid*,[2] an acid ester of sulphuric acid with carbohydrate, containing also amino-acid residues When chondroitin sulphuric acid is boiled for a short time with acids, it is hydrolysed further to sulphuric acid and a sulphur free component *chondrosin*

The *melanins*, of which very little is known, form another group of compounds standing in close relationship to the proteins They are dark brown or black pigments occurring in hair and skin, and are widely distributed throughout the animal kingdom Products resembling naturally occurring melanins are obtained by the acid hydrolysis of almost all proteins, these dark products are grouped together under the name of *humin substances*

Constitution of the Proteins

Recent researches have given rise to considerable discussion regarding the possible occurrence of heterocyclic groups in protein molecules It is well known that diketopiperazines are found among the hydrolysis products of proteins and that cyclic compounds such as pyrazines and pyrroles are formed by methods of reductive disruption The difficulty is to determine whether these cyclic products exist as such in the protein or come into being as a result of the decomposition processes

I *Diketopiperazines*—Abderhalden has recently isolated a number of diketopiperazines from proteins by mild chemical or fermentative disruption These include *alanyl-glycine anhydride*, obtained by hydrolysing dog's hair with 1 per cent hydrochloric acid for eight hours in an autoclave at 150° to 160°, and *alanyl-leucine anhydride* and *alanyl-phenylalanine anhydride*, prepared in a similar manner from hog's bristles[3] The isolation of these compounds, according to Abderhalden,

[1] Compare P A Levene, *J Biol Ch*, 1917, **26**, 143 [2] For further details see Orgler and Neuberg, *Z physiol Ch*, 1903, **37**, 399 Levene and La Forge, *J Biol Ch*, 1913, **15**, 69, 155, 1914, **18**, 123, 1915, **20**, 433 [3] E Abderhalden and E Komm, *Zeit f physiol Chem*, 1925, **145**, 309

indicates the existence of diketopiperazine structures in the original proteins On the other hand, E Fischer, and also Brigl[1] and Abderhalden, have demonstrated the ease with which diketopiperazines are formed as secondary product from polypeptides

Abderhalden has obtained some confirmation of his views in the colour reactions given by diketopiperazines with picric acid, 3 5-dinitrobenzoic acid and similar compounds Such reactions are also given by most of the proteins and peptones, but not by polypeptides or amino-acids These conclusions, however, are opposed by various critics, including M Bergmann[2]

Methods of oxidative and more especially of reductive disruption have been utilised by Abderhalden Using sodium and amyl alcohol as reducing agents, he obtained piperazines from diketopiperazines, but not from polypeptides or amino-acids On applying this procedure to silk fibroin, silk peptone and gelatin, Abderhalden also succeeded in isolating piperazine derivatives, thus affording further evidence in support of the existence of diketopiperazine units in the proteins[3]

Against these views must be placed the facts that ordinary diketopiperazines have no tendency to polymerise,[4] nor to be attacked by ferments[5] (pepsin, trypsin, erepsin, or yeast proteases), in which respects they differ from most proteins Abderhalden's somewhat improbable suggestion that diketopiperazines are disrupted in the digestive juices without fermentative intervention has been refuted by Waldschmidt-Leitz, who points out that diketopiperazines have hitherto been isolated chiefly from silk fibroin and keratin, substances which are scarcely attacked in the gastro intestinal canal

II *Pyrroles* —It has long been known that pyrroles may be obtained from proteins by dry distillation or hydrolysis By the latter method, E Fischer isolated pyrrolidine carboxylic acid (proline) and hydroxy pyrrolidine carboxylic acid, and Hopkins obtained the indole derivative tryptophane More recently, Troensegaard[6] has advanced the suggestion that proteins are built up mainly of heterocyclic units, especially of pyrrole rings, and has devised methods of testing this hypothesis The proteins (principally gliadin, gelatin, casein, and the proteins of blood) were first stabilised by acetylation and then subjected to vigorous reduction with sodium and amyl alcohol The products so obtained were of a decided heterocyclic character and consisted largely of pyrroles

III *Other ring systems*, such as those present in the oxazolines and oxazoles, are also considered by some chemists to enter into the structure of proteins[7]

[1] P Brigl, *Ber*, 1923, 56, 1887 [2] E Abderhalden and Komm, *loc cit*, M Bergmann, *ibid*, 1925, 144, 277 [3] E Abderhalden und F Schwab, *Zeit f physiol Chem*, 1925, 148, 254 [4] Polymerisable methylene diketopiperazines have, however, been obtained by M Bergmann, A Miekeley and F Kann, *Ann*, 1925, 445, 17 [5] Abderhalden and Goto, *Fermentforschung*, 1923, 7, 169, Waldschmidt-Leitz and A Schäffner, *Ber*, 1925, 58, 1356 [6] N Troensegaard, *Zeit f physiol Chem*, 1920, 112, 86, 1923, 127, 137, 142, 304, 1929, 184, 147 F Klumann, *Chemical Reviews*, 1927, 4, 102 See also Troensegaard, "Über die Konstitution der Eiweissverbindungen," *Zeit angew Chem*, 1925, 38, 623 [7] M Bergmann and co workers, *Zeit f physiol Chem*, 1925, 148, 108 P Karrer and co workers, *Helv Chim Acta*, 1924, 7, 763, 1925, 8, 205

Despite these interesting researches, the problem of protein structure still remains undetermined. Against the newer ideas must be placed certain biological facts which indicate a fundamental relationship between proteins and amino-acids. Each living organism disrupts proteins into polypeptides and amino-acids, and again builds up its own protein matter from a mixture of amino-acids. In addition, every ferment action is linked up with the liberation of free amino and carboxyl groups. The probability, therefore, is that these final products into which the organism disrupts proteins and from which it again synthesises them, form the chemical units from which the protein molecules are themselves elaborated. There still remains the possibility that a small group of proteins, including silk fibroin and keratin, contain a large proportion of diketopiperazine units, thus explaining their resistance towards enzymes.

X

Chlorophyll and other Plant Pigments[1]

The following chapter is devoted to the chemistry of the colouring matters of plants and is divided into two sections, the first dealing with the pigments of leaves and the second with those of flowers and berries. This subject was first successfully attacked by Willstatter and his co-workers.

CHLOROPHYLL[2]

Until recently chlorophyll as a chemical substance was unknown. It was uncertain whether the green colouring matter of leaves was represented by one compound, by several similar compounds, or by a great number of substances. The present state of our knowledge may be summarised as follows.

It has now been established that the chloroplasts consist of a colloidal mixture of colourless substances with four pigments, viz., two closely related chlorophyll colouring matters and two yellow pigments. These compounds are:—

1. *Chlorophyll*-a, $C_{55}H_{72}O_5N_4Mg$, a bluish-black solid giving greenish-blue solutions.
2. *Chlorophyll*-b, $C_{55}H_{70}O_6N_4Mg$, a greenish black solid giving pure green solutions.
3. *Carotene*, $C_{40}H_{56}$, an orange-red crystalline substance.
4. *Xanthophyll*, $C_{40}H_{56}O_2$, a yellow crystalline substance.

These four pigments were found in every plant examined, irrespective of its botanical classification.

[1] See R. Willstatter, *Ber.*, 1914, 47, 2831; *J. Am. C. S.*, 1915, 87, 323. [2] Compare Willstatter and Stoll, *Untersuchungen über Chlorophyll* (Springer, Berlin, 1913).

Chlorophyll contains 2·7 per cent of magnesium and gives an ash of pure magnesia, phosphorus and iron being absent. On hydrolysis it yields the alcohol *phytol*, $C_{20}H_{40}O$ (see p. 146), in quantities corresponding to about a third part of its molecule. The other hydrolysis product is a nitrogenous carboxylic complex containing four pyrrole nuclei. The constitution of this fragment has been determined by an examination of the decomposition products *phytochlorin*-e, obtained from chlorophyll-*a*, and *phytorhodin*-g, obtained from chlorophyll-*b*. The former is olive-green in ethereal solution, and the latter red.

Fresh leaves contain about 2 parts per 1000 of chlorophyll-*a*, ¾ of a part of chlorophyll *b*, ⅓ of xanthophyll, and ⅙ of carotene.

A great deal of information relating to the constitution of chlorophyll has been deduced by Willstatter from the behaviour of the decomposition products obtained by the action of acid and alkali on the parent compound.

Decomposition of Chlorophyll by Alkalis and Acids[1]—Under the influence of an alkali, chlorophyll yields phytol and the alkali salts of carboxylic acids. The salts are soluble in water and have a chlorophyll-green colour.

Gentle treatment with acid, on the other hand, leads to a different part of the molecule being attacked. No salt-forming groups are produced in this case and thus no hydrolysis has occurred, but the reaction is accompanied by a colour-change from chlorophyll-green to olive-green. The component of chlorophyll which is detached by alkalis is therefore not affected by acid under these conditions, and conversely, a characteristic group of atoms which is present in chlorophyll and the above alkali salts is attacked with surprising ease by acids.

From the examination of these and other degradation products obtained by the action of acids and alkalis on crude chlorophyll, Willstatter was able to gain so much information concerning the chlorophyll molecule that when the colouring matter was finally isolated in the pure state its investigation revealed nothing new.

The chlorophyll-green carboxylic acids (of the *a* and *b* series) formed by hydrolysing the crude alcoholic extract of leaves with alkali are known as **chlorophyllins**. Although somewhat unstable, they can be separated from the hydrolysis mixture in a more or less pure condition. These compounds contain magnesium, which is not present in the ionisable state but is assumed to be part of a metallic "complex". While the group containing magnesium is very sensitive towards acids, it is comparatively stable to alkalis. On being heated at temperatures up to 240° with concentrated alcoholic alkali,

[1] The various degradation products of chlorophyll mentioned in this chapter are summarised in a table on p. 783.

the chlorophyllins give rise to a series of crystalline decomposition products possessing magnificent colour and strong fluorescence.

The product first formed contains three carboxyl groups, and with progressive action this number is reduced to two and finally to one. All these acids are grouped together under the name of **phyllins**, and contain one atom of magnesium to every four atoms of nitrogen. Some of them are named from their colour, as in the case of *glaucophyllin* and *rhodophyllin*, which are respectively blue and red.

The carboxyl-free parent compound is known as **aetiophyllin**, and has the composition $C_{31}H_{31}N_4Mg$. It is obvious that the oxygen atoms present in the carboxyl groups have no part in the formation of the metallic complex, for which purpose the nitrogen atoms alone are available. The magnesium is therefore supposed to be united to nitrogen by principal and subsidiary valencies, as indicated in the following formula:

$$\begin{array}{c} Mg \\ // \\ \underbrace{N\,N}\;\underbrace{N\,N} \\ C_{31}H_{31} \end{array}$$

Aetiophyllin

Under the influence of acids all phyllins lose magnesium to yield compounds known as **porphyrins**. Except in the case of aetiophyllin, which contains no carboxyl group, the resulting products are carboxylic acids with basic as well as acidic properties. They are distinguished by use of the prefix corresponding to the phyllin from which they are derived.

The behaviour of the phyllins towards acids throws some light on the action of acids on a solution of chlorophyll itself. Under this treatment the colour of the chlorophyll changes to olive-green and the fluorescence diminishes. The chlorophyll derivative so obtained is known as *phæophytin*. As will be seen later, this is a mixture of the two closely related compounds, phæophytin-*a* and -*b*. It contains no magnesium and is very easily prepared by treating crude alcoholic chlorophyll solution with oxalic acid, when the phæophytin is precipitated almost quantitatively and in a practically pure condition. In this manner it may be isolated in large quantities in the laboratory from dried, finely ground leaves of the stinging nettle. Phæophytin is a wax-like substance possessing weakly basic but no acidic properties. In the colour of its solutions it is quite different from chlorophyll, but the resemblance reappears as soon as a metal capable of entering into complex union is introduced into its molecule. For example, chlorophyll-*a* can be regenerated from phæophytin-*a* by treating the latter with an excess of methyl magnesium iodide.

On hydrolysis with alkalis phæophytin behaves as a wax, breaking up into phytol, $C_{20}H_{39}OH$ (see p 146), and acids of high molecular weight, containing nitrogen and 34 carbon atoms A similar change is undergone by chlorophyll itself under the influence of alkalis, but in neither case is this the whole reaction Phæophytin and chlorophyll both contain the grouping $—COOCH_3$, which is also attacked on further hydrolysis In addition, the action of alkalis brings about a peculiar transformation accompanied by a remarkable change of colour, passing through what has been termed the "brown phase" This is probably due to complex structural changes in the chlorophyll molecule

Chlorophyll contains a constant quantity of phytol, corresponding to about $\frac{1}{3}$ of the molecule, but after extraction from plants it was observed that the phytol content of the product was frequently low and in some cases fell to zero A preparation of low phytol content was found to be the best source for the isolation of "crystalline chlorophyll," discovered as early as 1881 by Borodin This forms a mass of microscopic plates differing strongly from ordinary or amorphous chlorophyll in appearance [1]

The connection between the low phytol content of chlorophyll preparations and the simultaneous formation of crystalline chlorophyll was explained by Willstatter in 1907 It was observed that the phytol content of many leaves was normal when they were rapidly extracted with alcohol, but that if the extract was allowed to stand in contact with the finely powdered dried leaves, as is the case during a prolonged extraction, the phytol content was abnormally low Now chlorophyll is accompanied in the green parts of the plant by an enzyme *chlorophyllase* This is an esterase and is able to bring about alcoholysis of the chlorophyll, with liberation of phytol, which readily dissolves in the alcohol used for extraction Crystalline chlorophyll is similar to ordinary chlorophyll in composition, but whereas the latter is an ester of the acid chlorophyllide, $[RMg]\begin{cases} COOCH_3 \\ COOH \end{cases}$, with phytol, the former is an ester of this acid with the particular alcohol used for the extraction In other words, during the extraction process the phytyl group has been replaced by a methyl or ethyl group The enzyme chlorophyllase occurs widely distributed in plants, but in very variable amounts It is used in quantity for preparative purposes From

$$\underset{\text{Chlorophyll}}{[RMg]\begin{cases} COOCH_3 \\ COOC_{20}H_{39} \end{cases}} \xrightarrow{EtOH} \underset{\text{Ethyl chlorophyllide}}{[RMg]\begin{cases} COOCH_3 \\ COOC_2H_5 \end{cases}} \xrightarrow[\text{alkali}]{\text{Cold}} \underset{\text{Chlorophyllin}}{[RMg]\begin{cases} COOH \\ COOH \end{cases}}$$

(R contains carbon, hydrogen, oxygen and nitrogen)

[1] Willstatter and Benz, *Ann*, 1907, 358, 267

either fresh or dried leaves almost the whole of the chlorophyll may be isolated in the form of the ethyl or methyl derivatives, known respectively as **ethyl** and **methyl chlorophyllides** On prolonged hydrolysis with alkalis these yield the free carboxylic acid or chlorophyllin

A point of special interest is that the above process can be reversed, chlorophyll having been built up from phytol and chlorophyllide under the catalytic influence of chlorophyllase

The nitrogenous carboxylic acids formed together with phytol by the hydrolysis of phæophytin are coloured compounds and also possess basic properties Investigations at first led to the isolation of a large number of these hydrolysis products, which could be divided into two groups the **phytochlorins**, giving olive-green solutions in indifferent solvents, and the **phytorhodins** giving a magnificent red colour Owing to their large number, the individual compounds were distinguished by letters prefixed by the group name Finally, however, two well-defined crystalline products were obtained from phæophytin, viz, phytochlorin-*e*, $C_{34}H_{34}O_5N_4$, and phytorhodin-*g*, $C_{34}H_{32}O_6N_4$

Phytochlorin e is a tricarboxylic acid, containing two free carboxyl groups and one present in a lactam grouping *Phytorhodin*-g is a tetracarboxylic acid, containing either two or three of these groups in the free state From the formation of these two products it is concluded that phæophytin, and hence also chlorophyll, is a mixture of two components, one of which yields phytochlorin *e* as a degradation product and the other phytorhodin-*g*

Willstatter and his collaborators attacked the problem of separating this mixture of components by both physical and chemical methods A method used with chlorophyll solutions, crystalline chlorophyll, and phæophytin, takes advantage of the unequal distribution of the pigments between immiscible solvents, such as aqueous methyl alcohol and petroleum ether, or in the case of the difficultly soluble phytol-free compounds by use of methyl alcohol and ether + light petroleum After numerous repetitions of this process, the two components were eventually isolated in the pure state This operation was successfully applied to chlorophyll, as well as to its magnesium-free derivatives Another method, which is only available for the magnesium-free compounds, involves fractionation with hydrochloric acid (Willstatter and Mieg)

Isolation of Chlorophyll and Separation into its Components—The isolation of chlorophyll, which was accomplished in 1911 by Willstatter and Hug,[1] is based on the colorimetric estimation of its solutions and their systematic concentration by treatment with immiscible solvents In this manner it was possible to remove the colourless and yellow substances from the chlorophyll with which they are

[1] Willstatter and Hug, *Ann*, 1911, 380, 177

found The chlorophyll content (8 to 16 per cent) of the original extract could thus be raised to 70 per cent At a certain stage in the purification, the chlorophyll, although still readily soluble in a mixture of petroleum ether and alcohol, is no longer soluble in pure petroleum ether On washing out the ethyl or methyl alcohol from such an extract, the chlorophyll separates out and can be purified by solution in ether and reprecipitation with petroleum ether

On the large scale, the starting material in the preparation of chlorophyll is usually the dry, powdered leaves of the stinging nettle[1] A layer of the finely ground leaves, about 2000 gms, is placed on a large stoneware filter and extracted with 85 to 90 per cent alcohol, or better with 80 to 85 per cent acetone The pigment is extracted almost quantitatively, a yield of about 13 gms being obtained The method may also be applied to fresh leaves

While carrying out this process for the isolation of chlorophyll, it was observed that the two components divided themselves unequally between methyl alcohol and petroleum ether Systematic fractionation in this way finally led to the isolation of the components *a* and *b* in the homogeneous condition **Chlorophyll-*a*** is bluish green in colour and **chlorophyll-*b*** yellowish-green, but despite this difference the compounds are very similar in composition and represent different stages of oxidation Probably the *b*-compounds are derived from those of the *a*-series by the replacement of two atoms of hydrogen by one of oxygen, as shown in the following formulæ

Chlorophyll a, $C_{55}H_{72}O_5N_4Mg$ | *Chlorophyll* b, $C_{55}H_{70}O_6N_4Mg$

or $(C_{32}H_{30}ON_4Mg)\left\langle\begin{array}{l}COOCH_3\\ COOC_{20}H_{39}\end{array}\right.$ | or $(C_{32}H_{28}O_2N_4Mg)\left\langle\begin{array}{l}COOCH_3\\ COOC_{20}H_{39}\end{array}\right.$

This is in complete agreement with the difference in the compositions of phytochlorin-*e* and phytorhodin-*g*, the former of which is produced from chlorophyll-*a*, and the latter from chlorophyll-*b*

Owing to the high molecular weight of chlorophyll, the analytical evidence upon which these conclusions are based is somewhat uncertain, but additional support for the above relationship between the two components is given by other experimental results

Constitution of Chlorophyll[2]

In these pages it is only possible to deal with the more important conclusions which have been reached regarding the constitution of chlorophyll, for further details reference should be made to the original work of Willstatter[3] It has been mentioned that, under the influence of alkali, chlorophyll-*a* and -*b* each give rise to several series

[1] See Willstatter and Stoll, *Untersuchungen über Chlorophyll*, p 75 Willstatter and Isler, *Ann*, 1911, 380, 154, 1912, 390, 269 [3] Willstatter, *Ber*, 1914, 47, 2856

of phyllins and porphyrins (see p 778) The removal of the last carboxyl group in the phyllins and porphyrins is effected by heating them in small quantities with soda lime[1] In this manner the derivatives of chlorophyll *a* yield the same *ætiophyllin*, $C_{31}H_{34}N_4Mg$, and *ætioporphyrin*, $C_{31}H_{36}N_4$, as those of chlorophyll *b* These two degradation products are crystalline compounds and possess the general properties of the phyllins and porphyrins already described

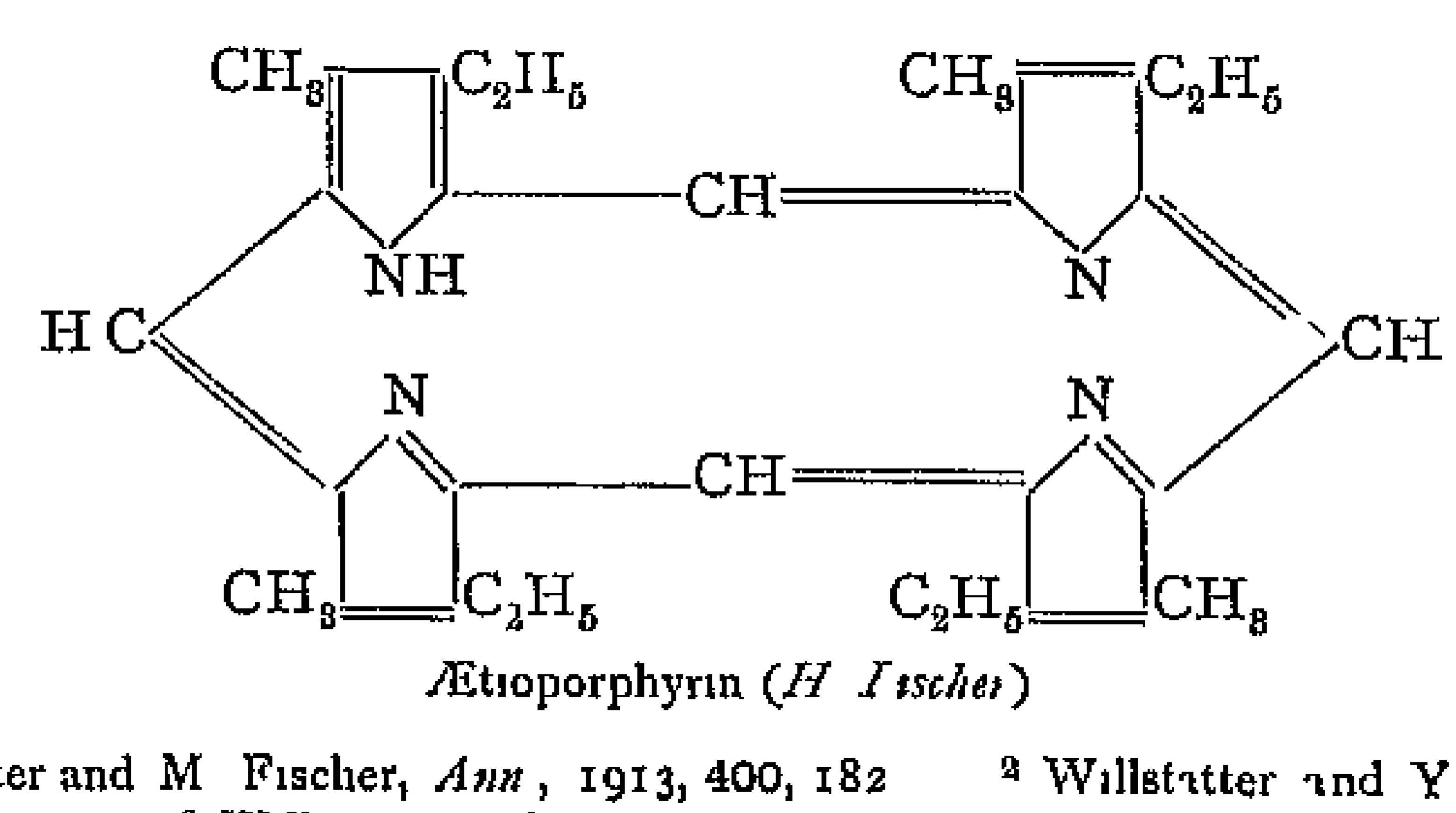
The study of the constitution of chlorophyll may be simplified by first confining our attention to that of ætioporphyrin Information on this point can be gained from an examination of the oxidation and reduction products of chlorophyll derivatives

On oxidation,[2] phylloporphyrin yields the same products as were obtained by the degradation of the colouring matter of blood, viz, *methyl ethyl-maleinimide*, in more than one molecular proportion, and a molecular proportion of *hæmatic acid* (p 573)

On reduction,[3] porphyrins yield *hæmopyrrole*, which has also been isolated as a decomposition product of the colouring matter of blood Hæmopyrrole is known to be a mixture of several components (see p 572)

From these and other facts it is concluded that ætioporphyrin is a tetrapyrrole, *i e* it is built up from four pyrrole nuclei The number of hydrogen atoms in the molecule is remarkably low, and the pyrrole nuclei must be united and substituted in such a manner that they contain 8 hydrogen atoms less than if they were joined by single bonds This may be explained by assuming the existence of double bonds or of further ring closure

A remarkable series of researches on the porphyrins and related compounds has been carried out within the last few years by Hans Fischer This has culminated in the synthesis of a number of compounds of this group, including ætioporphyrin and ætiophyllin[4] The synthetic ætioporphyrin proved identical with the product from natural sources in its spectrum, crystallographic form and other properties



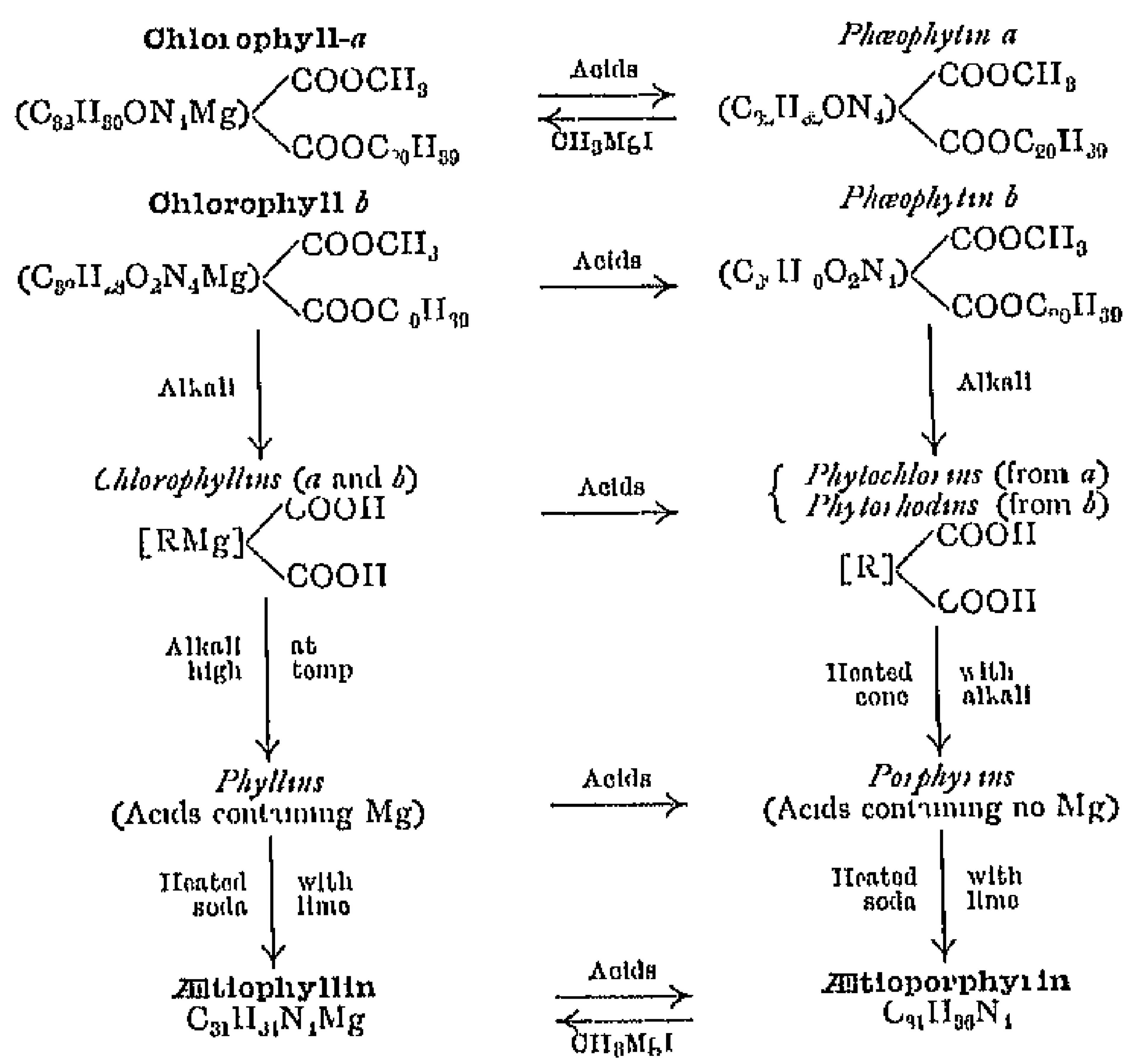
Ætioporphyrin (*H Fischer*)

[1] Willstätter and M Fischer, *Ann*, 1913, 400, 182 [2] Willstätter and Y Asahina, *Ann*, 1910, 378, 227 [3] Willstätter and Y Asahina, *Ann*, 1911, 385, 188 [4] H Fischer and Klarer, *Ann*, 1926, 448, 178

The problem of the constitution of these compounds became of still greater interest when it was shown by Willstatter and H Fischer that the colouring matter of blood could also be degraded to ætioporphyrin Hæmin and chlorophyll can thus be converted into a common decomposition product, which is still closely related to the parent compounds For the conclusions arrived at by Willstatter regarding the colouring matter of blood, reference should be made to the original paper [1] The following points, however, may be noted

Although chlorophyll and hæmin can be referred to the same basis, ætioporphyrin, Willstatter does not consider that this necessarily indicates a close constitutional connection between chlorophyll and hæmin Chlorophyll contains magnesium, the colouring matter of blood, on the other hand, contains iron The former is an ester of phytol, but the latter is combined with the protein globin Differences corresponding to such dissimilar functions are probably due to considerable differences in the molecular constitution of the pigments, and these differences only disappear after far-reaching degradation of the two molecules

CHIEF DECOMPOSITION PRODUCTS OF CHLOROPHYLL



Note —In order to simplify the formulæ in the above summary, the same letter R has been used to represent a number of different groups of atoms corresponding to the *a* and *b* series

[1] Willstatter, *Ber*, 1914, 47, 2863.

Carotinoids

The carotinoids, or yellow constituents accompanying the green colouring matter of leaves, are found associated with chlorophyll in the chloroplasts. They are widely distributed in plants, and are obtained as by-products in the preparation of chlorophyll.

All green leaves contain two nitrogen-free crystalline pigments, which possess many properties in common but may be separated by taking advantage of their different solubility in certain solvents. One of these pigments is **carotene** (carotin), an unsaturated hydrocarbon,[1] $C_{40}H_{56}$, which is also present in the carrot and in butter. According to recent researches it is intimately related to vitamin A, possibly being transformed into the latter in the body. The other constituent, **xanthophyll**, $C_{40}H_{56}O_2$, appears from its properties to be an oxide of carotene. The hydrocarbon is comparatively soluble in petroleum ether, whereas the oxygen compound is only soluble in alcohol.

A third carotinoid, **fucoxanthin**, $C_{40}H_{54}O_6$, is present in brown algæ, in which it partly replaces the other two compounds. In chemical properties it resembles carotene and xanthophyll, but differs in its basic character, due to the presence of oxygen in an ether type of linkage.

Willstätter and Escher isolated **lycopene**, an isomeride of carotene, from a commercial extract of the fruit of the tomato plant (*Lycopersicum esculentum*), and Willstatter obtained a compound, **lutein**, from the yolk of hens' eggs. The latter was originally considered to be an isomeride of xanthophyll. In all probability however, xanthophyll is itself a mixture of isomerides, one of which is considered by Palmer[2] to be identical with lutein.

The constitution of these yellow pigments has not yet been completely determined. Lycopene appears to be an unsaturated compound of aliphatic type, since hydrogenation converts it into the paraffin, $C_{40}H_{82}$. Carotene, on the other hand, is believed to be a dicyclic derivative. It contains 11 double bonds and on catalytic hydrogenation yields a hydrocarbon $C_{40}H_{78}$. Oxidation with cold permanganate converts carotene into ionone, and it is therefore supposed to contain two ionone rings.[3]

Comparative Investigation of Leaf Pigments.—The investigation of the green colouring matter of a large number of plants has shown that in each case the same chlorophyll, consisting of the two components *a* and *b*, was present. The relative proportion of these two components also showed a great regularity, nearly three molecules of chlorophyll *a* corresponding to one of chlorophyll-*b*. The phæophyceæ form an exception, the chlorophyll from this source containing a much smaller proportion of chlorophyll-*b*.

[1] L. Zechmeister, *Ber.*, 1928, **61**, 566, 1534, 2003. Pummerer and Rebmann, *ibid.*, p. 1099. R. Kuhn and A. Winterstein, *Helv. Chim. Acta*, 1928, **11**, 427. [2] For further information on this debatable question, compare *Carotinoids and Related Pigments*, Palmer (New York, 1922). [3] P. Karrer and co-workers, *Helv. Chim. Acta*, 1929, **12**, 1142; 1930, **13**, 1084.

The molecular proportion of the green to the yellow pigments (p. 776) was found to be approximately constant at 3 : 1, and the proportion of carotene to xanthophyll about 0.6 : 1.

A kilogram of dried elder leaves (corresponding to about 4 kilos of fresh leaves) was found to contain —

8.48 gms. chlorophyll, consisting of 6.22 gms. chlorophyll-*a* and 2.26 gms. chlorophyll-*b*,

1.48 gm. carotinoids, consisting of 0.55 gm. carotene and 0.93 gm. xanthophyll.

ANTHOCYANINS [1]

In this group are included the colouring matters of flowers and berries, which give rise to the wonderful variety of tints met with in the vegetable kingdom.

The extracts from flowers, like the crude chlorophyll solutions obtained from leaves, contain the colouring matter admixed with highly complex substances of a colloidal nature, which render the isolation of the somewhat unstable pigments a difficult problem. In this case, however, the separation can be accomplished by chemical methods.

The anthocyanins are phenolic in character and form metallic salts, but attempts to isolate them in the form of their lead salts were unsuccessful, since precipitation by lead acetate is not sufficiently specific to bring about a separation from the other products present.

Anthocyanins, however, although containing no nitrogen, also possess well-marked basic properties by means of which it has been found possible to effect their purification. They combine with mineral and organic acids to give well-defined crystalline salts. These salts are of the oxonium type, but they are less completely hydrolysed in solution than the salts of pyrones (p. 634).

The compounds of anthocyanins with acids are red in colour, free anthocyanins (which are regarded as phenol-betaines) are violet, and the alkali salts are blue. Many of the variations in the colours of flowers are due to the occurrence of anthocyanins in these three states.

The colour of anthocyanins fades in solution as the result of intra-molecular change. The free colour base liberated from the salts by hydrolytic dissociation becomes transformed into a carbinol (pseudo-base), owing to the migration of a hydroxyl group from oxygen to carbon. This change recalls the formation of rosaniline from fuchsine.

The anthocyanins are glucosides, which on heating with 20 per cent. hydrochloric acid are rapidly and completely decomposed into a sugar and the corresponding coloured components, known as **anthocyanidins**.

[1] See *The Natural Organic Colouring Matters*, by A. G. Perkin and A. E. Everest (Longmans, Green & Co.). Willstätter, *Ber.*, 1914, **47**, 2865; *Ann.*, 1915, **408**; 1917, **412**; *Ber.*, 1924, **57**, 1938. R. Robinson, *J. C. S.*, 1922, 1928. R. Robinson and R. Willstätter, *Ber.*, 1928, **61**, 2503. P. Karrer and co-workers, *Helv. Chim. Acta*, 1927, **10**, 5, 67; 1928, **11**, 513.

Willstatter and Everest showed that a mixture of anthocyanin and anthocyanidin could be separated by shaking with a mixture of amyl alcohol and dilute acid The glucoside is retained by the aqueous acid and the anthocyanidin passes quantitatively into the amyl alcohol

Methods of Isolation—In many cases anthocyanins may be isolated by extracting the flowers, or the skins of the berries, with alcohol or glacial acetic acid, followed by precipitation of the extract with ether and recrystallisation from hydrochloric acid

A second method consists in the precipitation of the anthocyanins in the form of their sparingly soluble crystalline *picrates*, a process which has also been used for isolating the vegetable alkaloids This method was first employed in the case of the colouring matter of the grape, and has since been successfully applied to the isolation of pigments of other berries and flowers From grape skins it is possible to obtain in a few minutes the fine red crystals of the anthocyanin picrate, and these, on treatment with a methyl alcoholic solution of hydrochloric acid, are converted into the anthocyanin chloride

Anthocyanins and Anthocyanidins—The first anthocyanin to be obtained in the form of its crystalline chloride was **cyanin**, the pigment of the cornflower[1] In the blue flower it is present as the potassium salt

The colouring matter of the rose has also proved to be identical with cyanin For preparative purposes the rose is a better starting material than the cornflower From the dried petals it is possible to obtain approximately 1 per cent of their weight as the crystalline cyanin chloride

On hydrolysis cyanin decomposes into **cyanidin** and two molecules of glucose

The colouring matter of the red whortleberry (*Vaccinium vitis idæa*), known as **idæin**, is also a derivative of cyanidin, being composed of one molecule of galactose with one of cyanidin

Cyanidin has the composition $C_{15}H_{10}O_6$, and its chloride, $C_{15}H_{11}O_6Cl$

The anthocyanin present in the scarlet pelargonium is a diglucoside of the anthocyanidin **pelargonidin**, $C_{15}H_{10}O_5$, which contains one oxygen atom less than cyanidin

The violet flowers of the delphinium (*Delphinium consolida*) contain the anthocyanin **delphinin**, which is of more complex structure On hydrolysis it decomposes into two molecules of glucose, two molecules of *p* hydroxy benzoic acid and one molecule of anthocyanidin The latter, which has been named **delphinidin**, gives a chloride of the formula $C_{15}H_{11}O_7Cl$, and thus contains one atom of oxygen more than cyanidin

Derivatives of delphinidin appear to be distributed in nature in

[1] Willstatter and Everest, *Ann*, 1913, **401**, 1

flowers and fruit of a deep violet or blue colour Willstatter and his co-workers have isolated four other anthocyanins, all of which are derived from methyl ethers of delphinidin

Œnin, the colouring matter of the grape, crystallises well and is a monoglucoside **Œnidin**, the corresponding anthocyanidin, possesses the formula $C_{17}H_{14}O_7$ On being warmed with hydriodic acid it loses two methyl groups and is converted into delphinidin, of which it is therefore a dimethyl ether

An isomeric dimethyl ether with a different arrangement of the methyl groups is **malvidin**, the anthocyanidin of the wild mallow, in which it occurs in union with two molecules of glucose

Myrtillidin, a monomethyl ether of delphinidin, has been obtained by hydrolysis of the two very similar anthocyanins occurring in the bilberry (*Vaccinium myrtillus*, Linn) and the stock rose or black mallow (*Althea rosea*) The anthocyanins from these sources are monoglucosides In this way the question as to the identity or otherwise of the anthocyanins of red wine and of bilberry has been solved These two compounds are readily distinguished by the intense violet coloration produced on adding ferric chloride to a solution of myrtillidin or its glucoside,[1] whereas no coloration is given by the anthocyanin of wine

Glutianin, an anthocyanin from blue gentian, has been shown to be a *p*-hydroxy-cinnamoyl-delphinidin monoglucoside[2]

The quantities of anthocyanins present in the different parts of plants vary within wide limits In the pelargonium and mallow, the proportion is as high as 6 5 to 7 5 per cent of the dried flowers, in the berries, however, it is much lower, amounting, for example, to 0 4 per cent of the dried skins of the red whortleberry

Constitution of the Anthocyanidins

The empirical composition of the anthocyanidins suggests that they are closely allied to the yellow mordant colouring matters so widely distributed in plants, and especially to the dye-stuffs of the flavone and flavonol series, the structure of which has been established by the analytical investigations of A G Perkin and others, and the syntheses of Kostanecki (see p 636)

Cyanidin in its neutral state is isomeric with luteolin and kampherol pelargonidin is isomeric with apigenin and galangin and delphinidin with quercetin and morin

When anthocyanidins are heated with alkalis they decompose to yield two aromatic disintegration products, one of which is a phenol and the other a carboxylic acid In this, as in many other respects,

[1] The same coloration is also given by delphinidin itself [2] P Karrer and R Widmer, *Helv Chim Acta*, 1927, 10, 67

they resemble the flavone derivatives, a fact which is of great importance in the determination of their structure The methylated anthocyanidins are more satisfactorily decomposed with hot dilute alkalis, thus avoiding demethylation

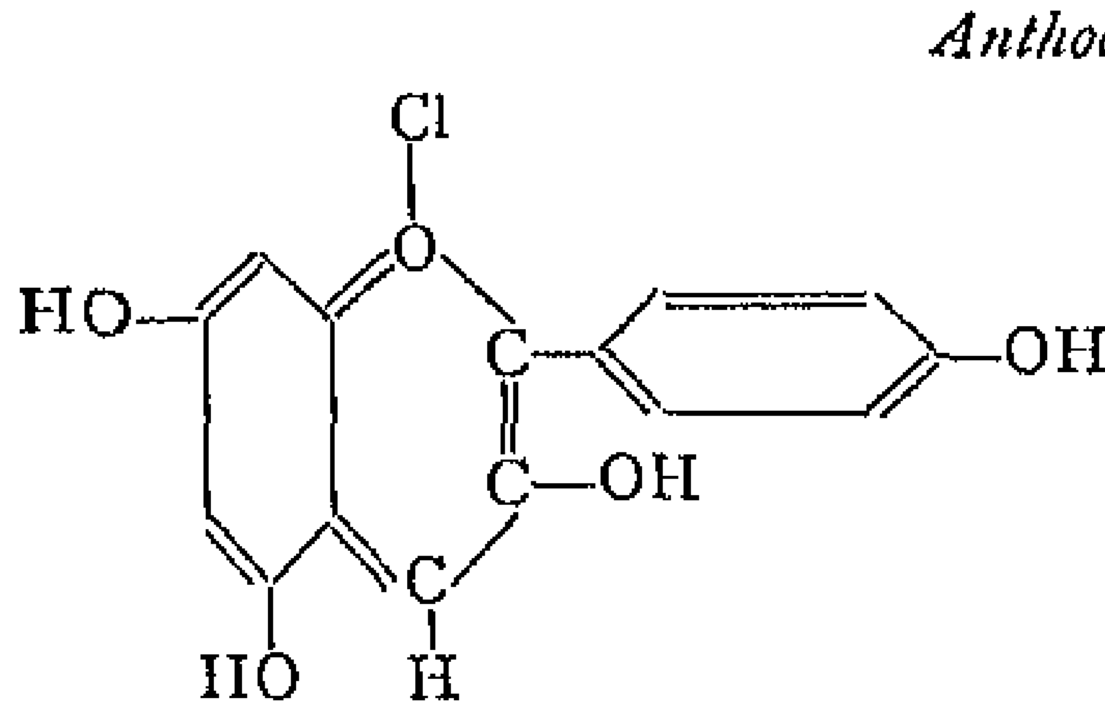
The phenolic component isolated from the anthocyanidins so far investigated has always been identified as *phloroglucinol* or its *mono methyl ether* The second decomposition product depends on the oxygen content of the original substance, *e g*,

Pelargonidin, $C_{15}H_{10}O_5$, gives *p*-hydroxy-benzoic acid,
Cyanidin, $C_{15}H_{10}O_6$, gives protocatechuic acid,
Delphinidin, $C_{15}H_{10}O_7$, gives gallic acid

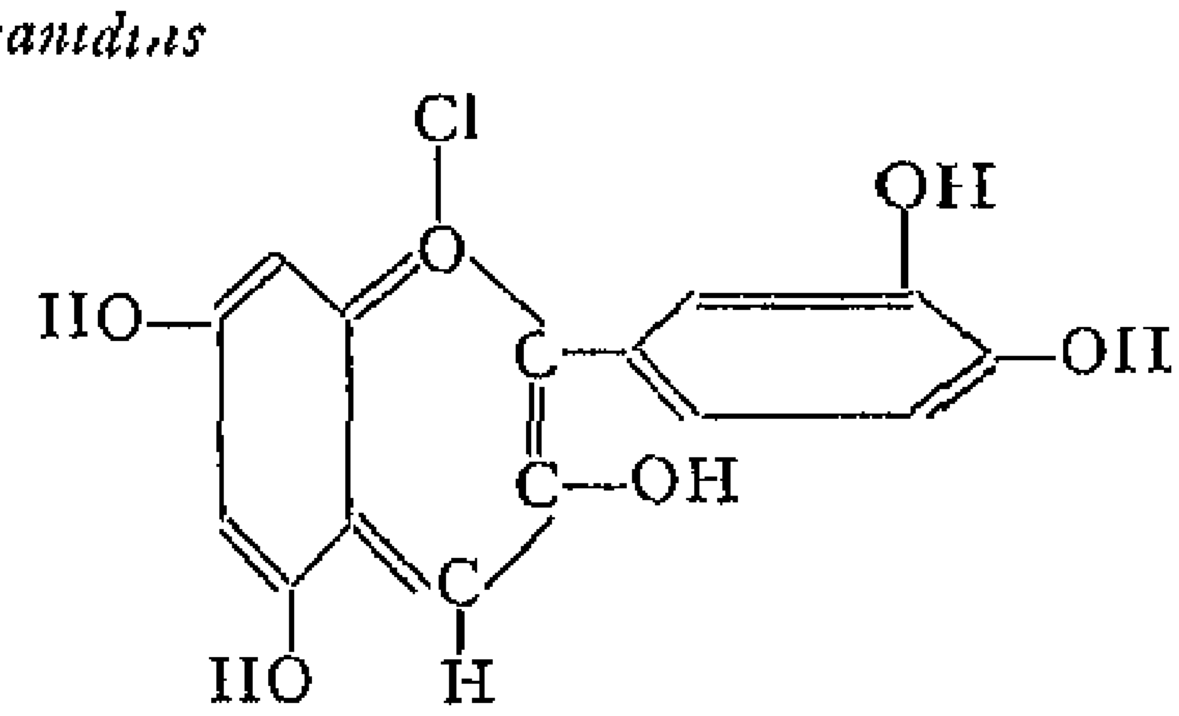
Of the methylated delphinidins, some give gallic acid and some the methyl ether of gallic acid

The anthocyanidins are oxonium compounds derived from benzopyrylium[1] The only structural difference between the flavones and the anthocyanidins is that the former are pyrones whilst the latter are pyrylium derivatives The structural formulæ assigned to a number of the anthocyanidins are given below

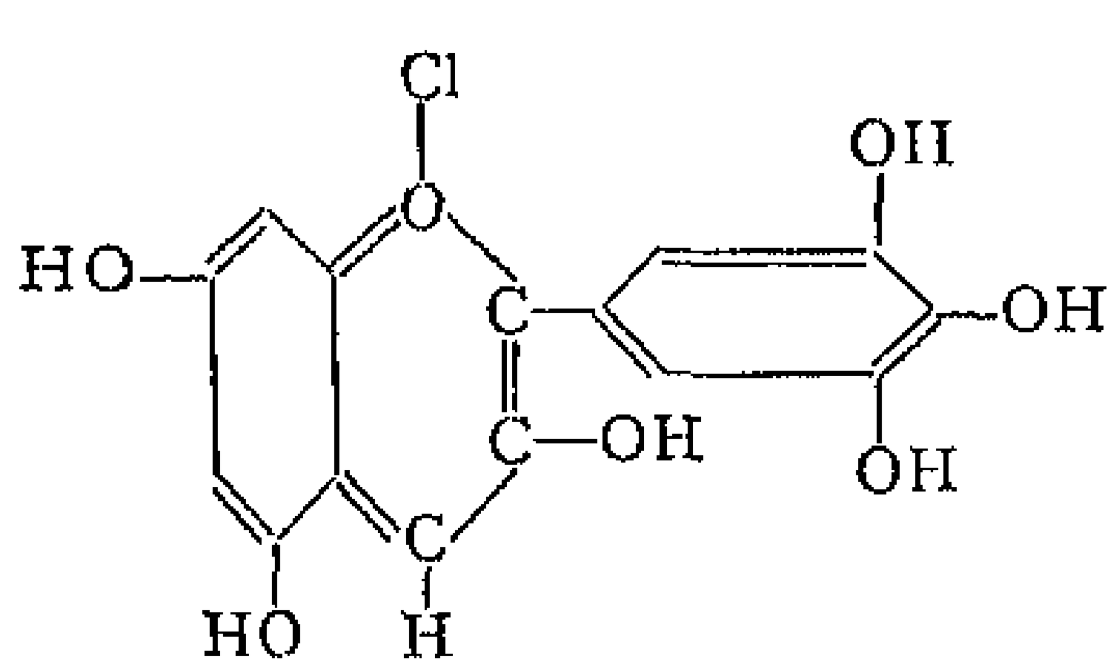
Anthocyanidins



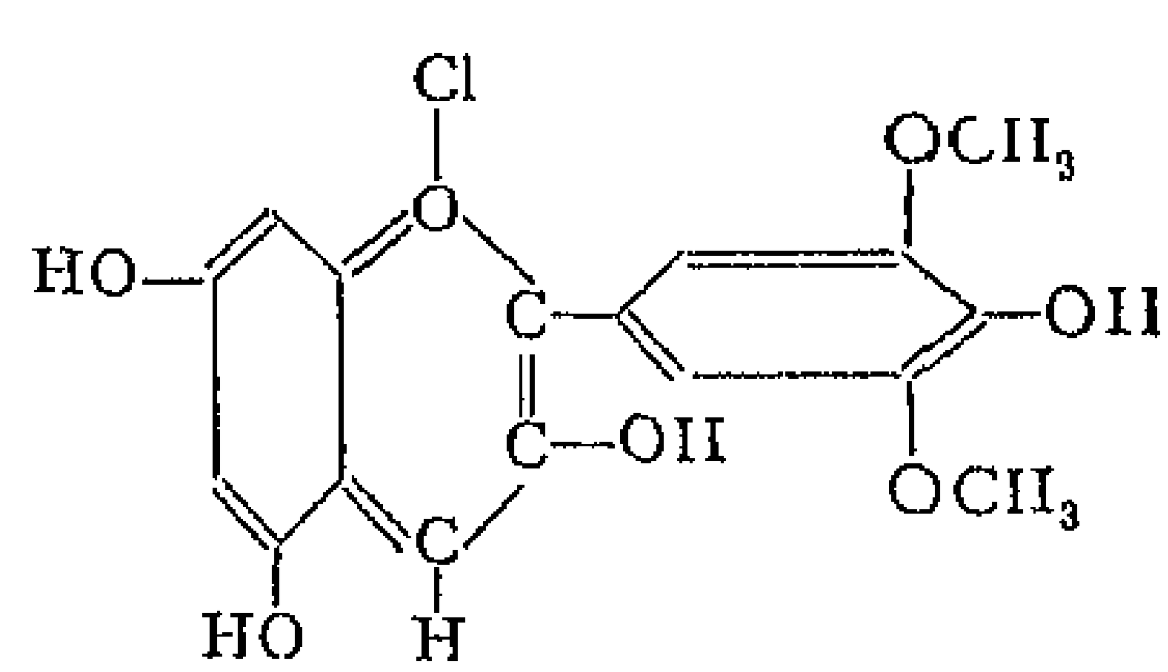
Pelargonidin chloride
(From the pelargonium)



Cyanidin chloride
(From the cornflower and rose)



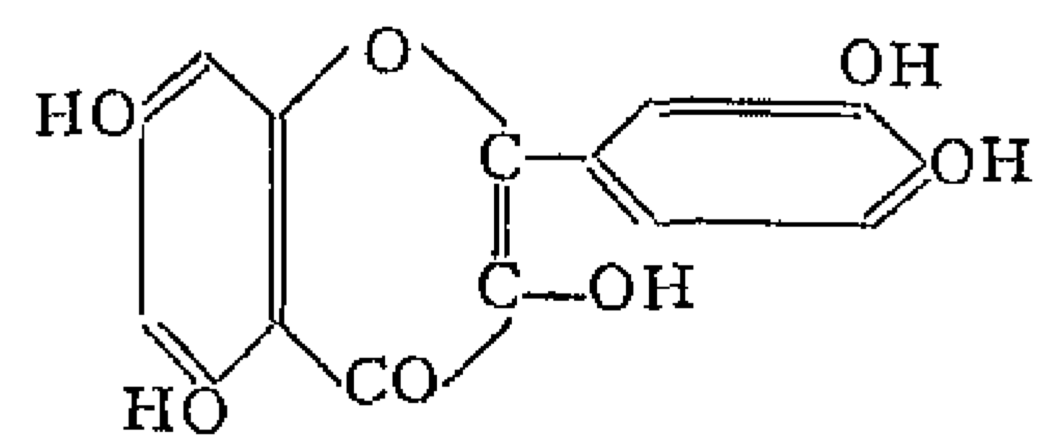
Delphinidin chloride
(From the delphinium)



Malvidin chloride, syringidin chloride[2]
(From the wild mallow)

[1] Benzo pyrylium was first synthesised by Decker and Fellenberg, *Ann*, 1907, 356, 281, 1908, 364, 1 [2] Synthesised by W Bradley and R Robinson, *J C S*, 1928, 1541

The constitutional formula which has been ascribed to cyanidin would suggest that the compound could be prepared from quercetin, and, in general, that the anthocyanidins could be obtained from the flavonols. This is readily understood by comparing the above structure of cyanidin chloride with the following formula for quercetin



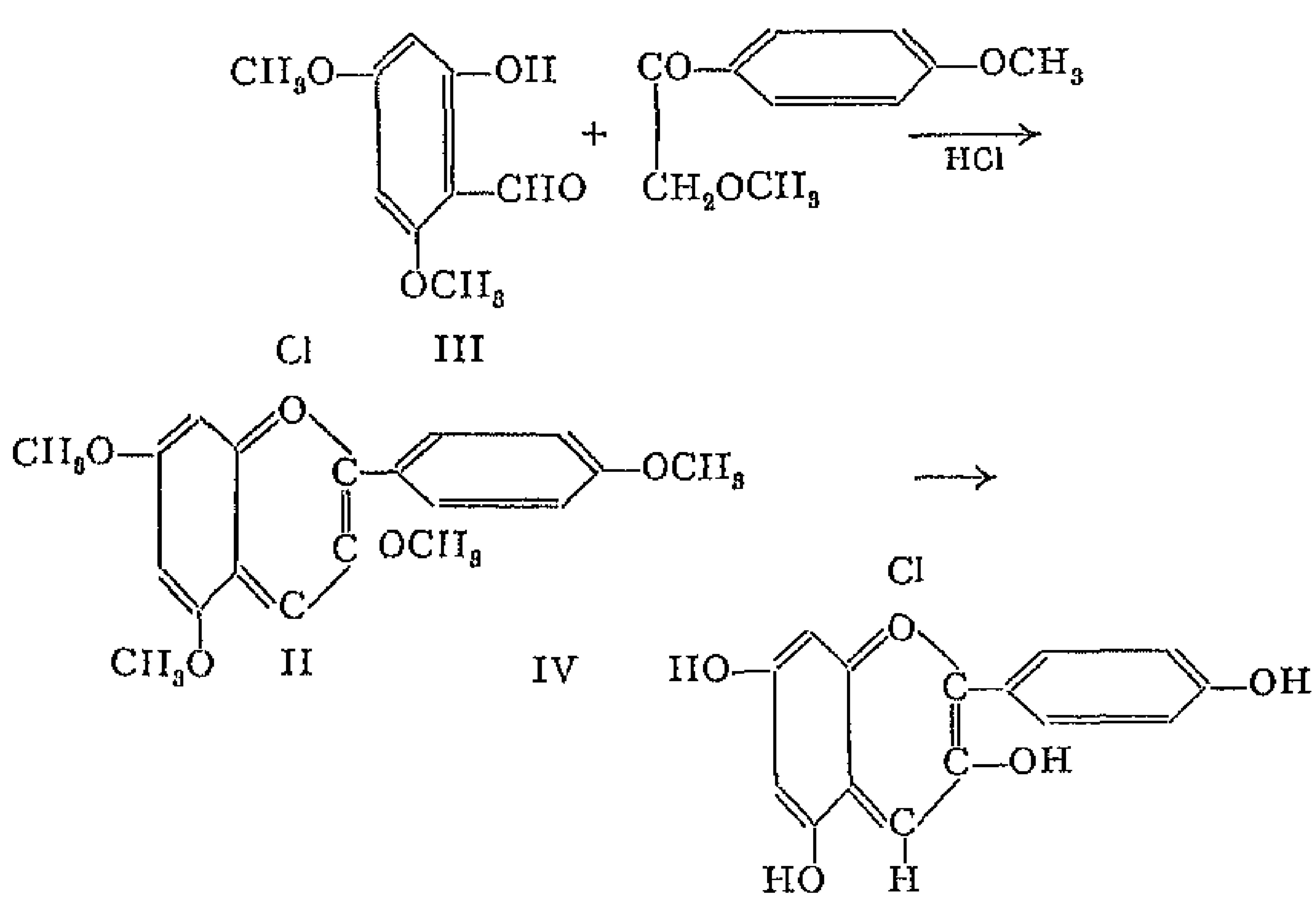
Quercetin

By the reduction of quercetin, Willstatter and Mallison[1] actually succeeded in obtaining a very small quantity of cyanidin

The structural formulæ assigned to these compounds has received further confirmation by a number of syntheses For example, pelargonidin has been synthesised by Willstatter and Zechmeister,[2] and more recently by Robinson and Pratt[3]

The synthesis of Robinson and Pratt was carried out as follows —

I II



2-Hydroxy-4 6-dimethoxy-benzaldehyde (I) and ω 4-dimethoxy-acetophenone (II) were condensed together in ethereal solution, in the

[1] *J C S*, 1914, A, i, 106, 1081 [2] *Ibid* [3] R Robinson and Pratt, *J C S*, 1924, 125, 190

presence of dry hydrochloric acid gas, to give tetramethyl-pelargonidin chloride (III) The latter was then demethylated to pelargonidin chloride (IV) by boiling with hydriodic acid in the presence of phenol

By applying similar methods to substances containing the glucose residue, A Robertson and Robinson have succeeded in synthesising naturally occurring anthocyanins[1]

ENZYMES

At the present time it is no easy task to give an exact definition of the word enzyme Perhaps the most satisfactory description is that of Bredig, who defines enzymes as catalytic substances which are elaborated by living organisms and are indispensable for the operation of their chemical processes This definition applies in the case of many enzymes, although Willstatter has recently again emphasised the fact that all enzymes cannot be classed as catalysts In general a chemical process may be described as an enzyme reaction when it proceeds more rapidly under the influence of a preparation obtained from living cells than without the addition of the active preparation, the reactions being otherwise carried out under similar conditions

For example, ethyl butyrate in aqueous solution is after a definite time hydrolysed to a measurable extent If the solution is treated with a glycerine extract of the pancreas, the same degree of hydrolysis is attained in a much shorter time, although the addition of a *boiled* glycerine extract does not materially influence the rate of hydrolysis Consequently fresh pancreas extract must contain an agent capable of greatly increasing the velocity of hydrolysis, *i e* an ester-splitting enzyme Particular importance is attached to the condition that an enzyme preparation must be free from living cells From this it follows that an enzyme is a lifeless physico-chemical system, the activity of which depends entirely on physico-chemical forces and which may therefore be investigated by purely physico-chemical methods Although more and more biochemical processes are now being recognised as enzyme reactions, in the majority of individual metabolic changes the enzymatic character of the action has not yet been proved The nonenzymatic changes of metabolism only proceed (within the narrow limits of temperature, acidity, etc, obtaining in the organism) under the influence of living cells As an example may be mentioned the deamination of amino-acids which occurs on a considerable scale in living animals Although liver freshly removed from the animal is capable, when artificially supplied with blood, of transforming alanine into lactic acid, liver tissue which has been mechanically subdivided or subjected to extraction processes no longer exhibits this property

[1] A Robertson and R Robinson, *J C S*, 1928, 1460

Detection of Enzymes—From the above definition of enzymes it follows that they can only be recognised by means of their catalytic influence Nevertheless, during recent years great progress has been made in our knowledge of individual enzymes O Warburg has employed photochemical methods in studying the absorption spectrum of a respiratory ferment and thus demonstrated its close chemical relationship to hæmatin These investigations have for the first time permitted a glimpse into the structure of an enzyme

In many enzyme reactions, the catalytic influence as measured by the velocity constant is largely proportional to the quantity of added enzyme preparation This observation can hardly be interpreted otherwise than on the assumption that the enzymes themselves represent substances, the relative amount of which can under certain conditions be measured quantitatively by its catalytic activity Quantitative methods of estimating yields of enzymes play a considerable rôle in modern preparative chemistry They provide a means of determining the degree of purity of a particular preparation and form the basis of analytical investigations of the purified product The results obtained are, however, somewhat limited since they only show that in the cases so far examined enzymes may be progressively freed from all known compounds without losing their activity

Preparation of Enzymes[1]—The first step in the preparation of an enzyme is to separate it from living cells This stage can often be avoided if a biological fluid, especially an active secretion such as gastric or intestinal juice, be employed as starting material, but owing to the troublesome operations necessary for the production of pure secretions, this type of work is restricted almost entirely to the digestive juices, which contain few enzymes and these in the form of a mixture unsuited to exact investigation Nowadays researches on the digestive juices rarely make use of the corresponding secretion as starting material, the sole possible method for the preparation of those enzymes which induce a deep-seated decomposition of biological substances is the extraction of the finely divided organ under consideration An important process is that due to E Buchner in which the cells are disrupted by pulverising the organ with quartz sand and kieselguhr The juice containing the ferments is then pressed out from the mixture under 300 atmospheres pressure This treatment does not merely consist in the simple disruption of the cell membranes, but in all probability complicated adsorption processes come into play.

[1] Reference may be made to the following works W M Bayliss, *The Nature of Enzyme Action* (Longmans, Green & Co, 1925) C Oppenheimer, *Die Fermente und ihre Wirkungen* (5th edition, Thieme, Leipzig, 1929), also, *Lehrbuch der Enzyme* (Thieme, 1927) H v Euler, *Chemie der Enzyme* (J Bergmann, Munich and Wiesbaden, 1922 27) E Waldschmidt Leitz, *Die Enzyme* (F Vieweg, Brunswick, 1926) A Fodor, *Das Fermentproblem* (Steinkopf, Dresden, 1929) J B S Haldane, *Enzymes* (Longmans, Green, 1930)

As is to be expected from the complexity of the biochemical reactions taking place in living organisms, the extracts obtained in this manner always consist of a mixture of different enzymes. From these extracts attempts are then made to remove impurities and other enzymes as completely as possible from the active substance, for which purpose use is made of adsorption, elution, salting out and other reversible processes and dialysis, only mild experimental conditions being employed. Stable dry preparations may often be successfully prepared by precipitation with alcohol or acetone and washing the precipitate with ether, although many enzymes lose much of their activity under this treatment.

Specific Influence of Enzymes.—The most noteworthy property of an enzyme is the specific nature of its reactions, which is frequently so strongly developed that the activity is exhibited solely towards one particular substance, known as the *substrate* of the enzyme. Extremely small modifications in the molecular structure of the substrate are sufficient to render it immune from attack. The fact that asymmetric substances in nature usually occur in the active and not in the racemic forms, finds one explanation in the preferential action of synthetic and disruptive enzymes on one of the two active isomerides of the asymmetric compound. Yeast, for example, is only able to ferment *d*-glucose, the laevorotatory sugar is not attacked.

The more carefully enzymes are studied, the finer are the degrees of specificity discovered, and the more certain becomes the conviction that many closely related reactions which have hitherto been ascribed to the catalytic activity of one and the same enzyme are in reality the result of several distinct enzymes. The same power of selectivity which determines the most complex functions of the organism may also be traced in the individual chemical processes of the living cell itself. Hence enzyme chemistry is of fundamental importance for the study of life processes.

The specific character of the enzymes, the importance of which for our knowledge of biological processes has been indicated above, has proved of great service in chemistry and medicine. Reference may be made to the biochemical method for the resolution of racemic compounds, to the use of enzymes in the classification of α- and β-glucosides, and to the simple quantitative micro-chemical determination of urea by means of urease.

Properties of Enzymes.—In a book of this kind space can only be found for a few general remarks on the properties of enzymes. Almost all the members of this class are very sensitive towards physical and chemical change. Heating for a short time above 50° leads in most cases to destruction, as does also treatment with the stronger alkalis, acids and salts of many of the heavy metals. Above all, the optimum conditions of reactivity of enzymes are subject to very sharp limitations,

as may be seen in the pronounced dependence of enzyme action upon acidity, which is so characteristic as to be employed for differentiating between closely related enzymes The optimum acidity for almost all enzymes lies, like the reaction of most of the body fluids, not very far from the neutral point An exception to this statement is found in the pepsinases, including the protein-disrupting ferment of the gastric juice which normally exists in the presence of hydrochloric acid

For the exercise of their specific influence many enzymes require activation by particular compounds (*activators*) which in some cases (*e g* amylase) may be simple salts, and in others (*e g* trypsin, a protein-splitting enzyme of the pancreas) are represented by complex products

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